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THE CLINICAL USE OF HYALURONIDASE IN HYPODERMOCLYSIS

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THE purpose of this report is to describe the clinical use of the enzyme hyaluronidase to facilitate the administration and absorption of large volumes of fluid given by hypodermoclysis.

It is now widely accepted that hyaluronidase, the mucolytic enzyme which acts on the mucopolysaccharide hyaluronic acid, is the "spreading factor" of Duran-Reynals[1] and McClean[2] (for reviews of hyaluronidase see Duran-Reynals,[3] Mann and Lutwak-Mann,[4] and Meyer[5]). In the absence of spreading factor, an intradermally injected indicator remains localized in a bleb from which it spreads at a slow rate; in the presence of hyaluronidase the solution spreads very rapidly, at a rate dependent mainly upon enzyme concentration, to an area determined principally by the volume of injection.[6] The spreading activity of hyaluronidase is due to the removal of a tissue barrier to fluid diffusion thought to be a hyaluronic acid gel present in the ground substance of the connective tissues which the enzyme depolymerizes. The spreading reaction is so rapid with optimal enzyme concentrations, that the bleb which results following injection is completely flattened within a minute or less.[3] While the spreading reaction of hyaluronidase has been studied most extensively in dermis, it is known that the enzyme produces a qualitatively similar response in subcutaneous tissues, muscle, and possibly in most tissues.[3]

Consideration of the spreading activity of hyaluronidase suggested that the enzyme might be useful clinically as an aid in fluid and drug administration by the subcutaneous or intramuscular routes where the volume of fluid administered is large relative to the tissue spaces available. Since the enzyme promotes rapid spreading, pain resulting from tissue distention produced by the injection of large volumes of fluid should be prevented or reduced. Where large volumes of fluid must be injected, hyaluronidase should increase the rate of fluid administration, since the injected fluid does not remain localized at the site of injection. Finally, the rate of circulatory absorption of the constituents of the injected fluid should be increased by hyaluronidase, since the

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injected material is in contact with a greater number of absorptive channels (capillaries and lymphatics) by virtue of the spreading produced by the enzyme.

While these actions of hyaluronidase suggest that the enzyme might be useful in a number of clinical problems involving fluid and drug administration, one instance where hyaluronidase appeared to offer special promise is in the facilitation of hypodermoclysis (first advocated by Sannella[7]). This method of fluid administration, as is well known, is painful, time consuming, and the administered fluid is generally absorbed at a slow rate. Despite the known disadvantages of hypodermoclysis, this procedure remains an important method for administering large volumes of fluid, particularly to infants and young children.

An investigation was therefore undertaken to study the possible clinical usefulness of hyaluronidase as an aid in hypodermoclysis. The investigation was carried out in the following steps. First, the effect of hyaluronidase on the administration of large volumes of fluid subcutaneously was studied in guinea pigs and rabbits. After it had been determined that hyaluronidase markedly facilitates the administration of subcutaneously administered fluid in experimental animals, hyaluronidase was administered to normal adult human volunteers to determine whether the enzyme produced untoward reactions. Finally, after it was determined that hyaluronidase was nontoxic to humans, it was administered to patients receiving hypodermoclysis.

EXPERIMENTAL

The spreading enzyme used in these experiments was a bovine testis hyaluronidase preparation prepared by the method of Madinaveitia,[8] and furnished as a dry powder by the Schering Corporation. The preparation contained approximately 20 turbidity-reducing units per milligram as evaluated by the assay method of Kass and Seastone.[8a] In most instances the enzyme was used directly after dissolution in 0.85 per cent sodium chloride, but in other instances a sterile enzyme solution which had been stored in the refrigerator for varying intervals of time ranging from one to four weeks was employed. The hyaluronidase preparation utilized in these studies is antigenic as evaluated by tests on guinea pigs and rabbits.

Effects of Hyaluronidase Upon Clysis in Guinea Pigs and Rabbits.—Although Sanella[7] has reported that testis hyaluronidase administered in conjunction with saline clysis in rabbits significantly increased the rates of fluid administration and absorption, the variability of the results obtained in his study does not provide strong evidence for these conclusions.

It seemed necessary, therefore, to reinvestigate the effect of hyaluronidase upon the administration of fluid subcutaneously. In an attempt to eliminate variations between animals, the effect of hyaluronidase was first compared by giving clysis with and without enzyme into the hind legs of the same animal. This procedure, however, was still not satisfactory, for it was observed that the position of the needle under the skin influenced the rate of fluid administration to a large degree. Since it is impossible to determine when two hypodermic needles are subcutaneously placed in exactly the same position relative to

tissue elements, the following procedure was adopted to eliminate variations due to point of injection: saline was administered by drip hypodermoclysis at a constant hydrostatic pressure; the hypodermic needle was fixed in place with adhesive tape and the rate of fluid entry was determined; after the rate of fluid intake became constant, hyaluronidase was then injected into the rubber tubing connecting the needle and the fluid reservoir without disturbing the position of the hypodermic needle. The change of fluid entry induced by hyaluronidase was noted, and the character of the swelling produced by saline administration before and after hyaluronidase administration was observed.

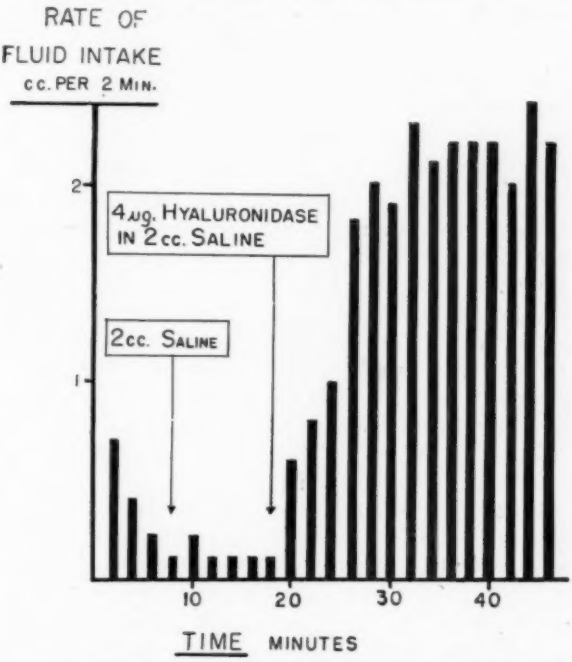

Fig. 1.—A typical experiment illustrating the intake of physiologic saline by the subcutaneous tissues of a guinea pig, in the presence and absence of hyaluronidase. At constant hydrostatic pressure (60 cm. of water) fluid was run into the tissues via a 26-gauge needle from a reservoir. It will be seen that the rate of fluid intake decreased in a short time as the injected area filled with fluid. When saline was injected into the rubber tubing connection between the needle and reservoir, no effect on fluid intake was obtained. When, however, 4 µg. of hyaluronidase were injected into the rubber tubing, the rate of fluid intake rapidly increased and this was maintained for the duration of the experiment.

The result of a representative experiment in a guinea pig, using the above procedure, is illustrated in Fig. 1. In this experiment, the hydrostatic pressure was held constant at 60 cm. of water, a 26-gauge needle was placed subcutaneously in one of the front paws; and the volume of fluid administered per two-minute interval was measured. Under these conditions, saline entered the subcutaneous tissues initially at a rate of 0.35 c.c. per minute in the first two minutes and then declined, so that after ten minutes the fluid intake was near zero. At this point it was noted that the injected fluid had formed a raised,

hard lump, well circumscribed around the point of injection. The pressure within the injected area of skin was almost sufficient to completely offset the hydrostatic pressure of the injection. To control the effect of an injection into the rubber tubing connection between the needle and the burrette upon the rate of fluid entry, 2.0 c.c. of saline were then injected into the rubber tubing. It will be seen that the injection of saline alone had no effect in increasing the rate of fluid administration during the next ten minutes. Then 2.0 c.c. of saline containing 4 μg. of hyaluronidase were injected into the rubber tubing connection. Immediately the rate of fluid intake was increased, and after six minutes had increased approximately three times over the initial rate of administration, i.e., before resistance due to the distention was established. After the introduction of hyaluronidase, the injected area, which had been hard and well circumscribed, became soft, easily movable, and spread considerably. During the next twenty minutes in which measurements were made, it was observed that the rapid rate of fluid administration induced by the enzyme was maintained.

This typical experiment demonstrates that the barrier to rapid diffusion in the subcutaneous tissues of the guinea pig can be removed by minute amounts of hyaluronidase, and thus the administration of fluid is facilitated. The effect of hyaluronidase to facilitate fluid administration can be evaluated in either of several ways. For example, during the twenty-four-minute interval after 4 μg. of hyaluronidase have been introduced, 22 c.c. of saline were administered; this represents a rate of administration equivalent to 0.92 c.c. per minute. In the absence of hyaluronidase, the average rate was 0.2 c.c. per minute. On this basis of comparison, the rate of fluid administration was increased 4.5 times by hyaluronidase. Perhaps a better manner of evaluating the effect of hyaluronidase would be to compare the time necessary to administer equivalent large volumes of saline in its presence and absence. To administer a volume of 22 c.c. of saline with hyaluronidase, twenty-four minutes was required; without hyaluronidase, it would have required approximately six hours to administer the same quantity of fluid, assuming that the rate of fluid intake in the absence of enzyme remained constant. On this basis, hyaluronidase increased the rate of fluid administration more than twelve times.

In seven other experiments using the above technique in guinea pigs, it was observed that maximal spreading effects were produced by the administration of 1 to 5 μg. of enzyme, as evidenced by the fact that subsequent addition of 100 μg. of hyaluronidase did not increase the rate of fluid intake over and above the rise induced by the initial dose. In five guinea pigs, minimal effects were produced by doses of 0.05 to 0.1 μg. of hyaluronidase.

In general, it was observed that the effect of hyaluronidase to facilitate clysis was significantly influenced by the resistance or the "tightness" of the tissues. When the initial resistance was high, hyaluronidase produced the largest increases in the rate of administration over the initial values. When the skin was "loose" (and the initial resistance was low) and the rate of fluid entry in the absence of enzyme was high, hyaluronidase, while acting, produced less

effect on the rate of fluid intake. This proved to be true with both rabbits and guinea pigs but this effect of hyaluronidase action in the subcutaneous tissues is best observed in comparing guinea pigs to rabbits. In the former species the subcutaneous administration of saline led to hard, tight swellings which did not spread readily as the injection was continued. In rabbits, the subcutaneous administration of saline without enzyme led to the development of softer, less well-circumscribed swellings, which spread much more easily than in the guinea pig.

Toxicity Studies on Hyaluronidase in Normal Humans.—With the demonstration that microgram doses of hyaluronidase markedly facilitate clysis in experimental animals, it was necessary, before clinical trial in patients, to test the possible toxicity of the enzyme preparation available to us. After preliminary testing satisfied us that our hyaluronidase preparation given in doses equivalent to 50 to 200 mg. per kilogram in guinea pigs and rats, and 20 to 50 mg. per kilogram in rabbits produced no toxic reactions, hyaluronidase was administered to twelve normal human volunteers (nine men and three women), in amounts assumed to be much higher than the doses which would be necessary for clinical use in hypodermoclysis. In the first test, seven adult males received 2 mg. hyaluronidase in a volume of 1.0 c.c. intradermally in one arm and 1 c.c. saline in the other arm as a control. Following the administration of 2 mg. of enzyme, no significant change in the complete blood count was noted during the following week. Blood pressure and pulse were not affected and no toxic action of hyaluronidase was evident. The only untoward effect evident was that in four of the seven subjects a dull aching pain associated with slight erythema developed at the sight of injection several hours after administration of hyaluronidase. The local reaction persisted for a variable period of time, but disappeared in twenty-four hours. The local reactions observed were in no way similar to the reactions characteristic of allergic hypersensitivity, which developed in a short time (fifteen to thirty minutes), exhibit a characteristic wheal with pseudopodia and a red flare on the periphery of the wheal, and are associated with itching. The local reactions observed in these patients injected with hyaluronidase were of a type commonly associated with the injection of foreign protein. Since the hyaluronidase preparation we utilized is only partially purified, and undoubtedly contains inert bovine testis protein, this result is not surprising.

In the next experiments, the effect of enzyme concentration upon spreading activity was studied in six normal adults to determine whether significant spreading activity could be obtained with dilutions of enzyme insufficient to produce the local foreign protein reaction. Three men and three women received separate intradermal injections of 0.2 c.c. of solutions of hyaluronidase varying from 1,000 to 0.1 μg. per cubic centimeter, in separate areas of the two arms. The time of wheal disappearance was utilized as a measure of hyaluronidase spreading activity and any local reactions which developed following injection were noted. Table I illustrates the results obtained. It will be seen that, while hyaluronidase in all of the concentrations used decreased the time of wheal disappearance over the appropriate saline control, as the concentration is increased,

TABLE I. THE SPREADING ACTIVITY AND THE LOCAL SKIN REACTIONS PRODUCED BY VARYING CONCENTRATIONS OF HYALURONIDASE IN ADULT HUMAN BEINGS

HYALURONIDASE (μG. PER C.C.*)	NO. SUBJECTS	MEAN TIME OF WHEAL DISAPPEARANCE (MIN.)	"FOREIGN PROTEIN" SKIN REACTIONS RESULTING FROM INJECTION OF HYALURONIDASE		
			SEVERE	SLIGHT	ABSENT
1000	6	0.20 ± 0.06†	3	2	1
100	6	0.78 ± 0.17	0	1	5
10	6	3.0 ± 0.70	0	0	6
1	6	6.1 ± 1.20	0	0	6
0.1	6	15.0 ± 5.6	0	0	6
0	6	65.0 ± 8.4	–	–	–

*All injections were administered intradermally in a volume of 0.2 c.c. of 0.9 per cent NaCl.

†Standard error of the mean.

the spreading response tends to approach a maximal value. Thus, while there is a large difference in time of wheal disappearance obtained by increasing the dosage from 0 to 0.1 μg. per cubic centimeter there is a progressively smaller increase in spreading as dosage is increased, so that there are only small differences between 100 and 1,000 μg. per cubic centimeter of enzyme. Of interest in this connection was the simultaneous finding that while local foreign protein reactions occurred in five of the six subjects receiving 1,000 μg. per cubic centimeter enzyme, there was only one case in which a local reaction was observed using the 100 μg. per cubic centimeter concentration, and none with the 10 μg. per cubic centimeter dose, despite the fact that almost equivalent spreading effects were obtained with the lower dosages.

TABLE II. THE FAILURE OF A TESTIS HYALURONIDASE PREPARATION TO PRODUCE HYPERSENSITIVITY IN SEVEN ADULT HUMAN BEINGS

SUBJECT	HYALURONIDASE INJECTED		DATE OF SCRATCH TESTS*
	AMOUNT (MG.)	DATE	
1	2.0 0.222	1/ 8/45 4/20/45	Negative on 2/4/45, 2/28/45, 4/20/45, and 11/18/45
2	0.200	1/ 8/45	Negative 4/1/45
3	2.0	1/ 8/45	Negative 3/8/45, and 4/1/45
4	2.0	1/ 8/45	Negative 4/1/45, and 11/15/45
5	0.222	4/20/45	Negative 11/18/45
6	0.222	4/20/45	Negative 11/18/45
7	0.222	4/20/45	Negative 11/18/45

*The solution used in the scratch tests contained 2.0 mg. per cubic centimeter of bovine testis hyaluronidase.

To determine whether the doses of hyaluronidase administered to our group of human beings produced hypersensitivity, "scratch tests" using a 2 mg. per cubic centimeter solution of bovine testis hyaluronidase were performed on seven subjects who had received hyaluronidase two to ten months previously. The results, shown in Table II, demonstrate that the bovine testis hyaluronidase given in amounts ranging from 2.222 to 0.222 mg. hyaluronidase was not antigenic in adult human beings.

Further Studies to Test Possible Toxicity of Hyaluronidase.—Although the above findings demonstrated that hyaluronidase, in the doses administered, was nontoxic and nonantigenic in normal adult human beings, before using hyaluroni-

dase clinically it was necessary to obtain information concerning the following additional points: (a) the minimal enzyme concentration required to facilitate absorption and administration of subcutaneously injected fluid in humans; (b) the duration of time necessary to reconstitute the tissue barrier to fluid diffusion removed by hyaluronidase; (c) the effect of a hyaluronidase clysis upon a distant localized infection, since it is possible that hyaluronidase, which facilitates spreading of bacteria as well as fluids, might promote the invasiveness of the bacteria and thus enhance the pre-existing lesion; (d) the possible toxicity of hyaluronidase in a patient with lowered resistance in contrast to an individual with normal resistance.

Information concerning (a), (b), (c), and (d) was obtained from studies in a congenital hydrocephalic patient who had localized infections. As is well known, hydrocephalics have a decreased resistance to infection and other stresses.

CASE 1.—A white female congenital hydrocephalic, hospitalized in the Pediatric ward at Hahneman Hospital since birth, weighed 6 lbs., 12 oz., eight days after delivery, and had a head measurement of 15 inches. At the time the study was initiated, the patient (103 days old) weighed 12 lbs., 8 oz., and the head measurement was 24 inches. While the patient took feedings well, the increase in body weight seemed to be due primarily to the increased fluid within the head, since the body size or development did not otherwise appreciably increase. The skin of the extremities was extremely thin and "loose" (it could readily be picked up). The patient had a noninfected meningocele on the spine, and had bilateral infected decubitus ulcers on the parieteal regions of the head. The infectious processes had been controlled prior to the initiation of the study by frequent boric acid irrigation and the application of dry merthiolate dressings. During the period of thirty-one days that this patient lived, four clysis with varying doses of hyaluronidase were administered and compared to comparable clysis in the absence of enzyme. The fluid administered in all instances was 5 per cent glucose in 0.85 per cent saline. During this interval, a complete blood count was taken daily and rectal temperature measurements made thrice daily. The infected areas on the head were noted carefully to determine whether hyaluronidase clysis at a site distant from the lesion promoted spreading of the infection.

To determine the influence of hyaluronidase upon facilitation of clysis, varying concentrations of enzyme were administered subcutaneously into one subscapular region. Leaving the needle in place, 50 c.c. of dextrose-saline was then injected subcutaneously into the enzyme-treated area. The time required to administer this volume of fluid using maximal pressure, the character of the lump produced by injection, and the time required for the complete disappearance of the injected swelling were noted and compared to the results obtained following the injection of 50 c.c. dextrose saline into the opposite shoulder.

The effect of 2,000 μg. hyaluronidase injected in a volume of 2 c.c. was first studied. Using this dose of enzyme in the right shoulder, it was observed that the injection was completed in 75 seconds; the area after injection was soft and easily movable, no seepage of fluid from the injection hole was noted, and the fluid spread within ten minutes so completely that there was no swelling indicative of injection. In the other shoulder, which had not been treated with enzyme, the time required for fluid administration was 2.5 minutes, the injected area was hard and tense, fluid oozed out at the point of injection, and the fluid was "absorbed" in 60 to 90 minutes. After one week, the effect of a 20 μg. dose of hyaluronidase in facilitating clysis was studied. One week later, the effect of a 2 μg. dose was similarly determined. It was observed that the 20 μg. dose produced an effect equivalent to the 2,000 μg. dose; the 2 μg. dosage produced only a questionable effect to facilitate hypodermoclysis.

The duration of the hyaluronidase action to facilitate spreading was determined by reinjecting the enzyme-treated areas at twenty-hour-hour intervals with 50 c.c. physiologic

saline and noting whether the clysis was administered easily, produced a soft swelling which spread readily, and was absorbed within fifteen to twenty minutes. The injection of a single, 2,000 μg. dose of enzyme facilitated clysis five days but not seven days after the initial enzyme injection. With the 20 μg. dose of enzyme, it was observed that the hyaluronidase effect to facilitate clysis was evident twenty-four hours after the initial injection, but unfortunately the entire duration of the residual activity of the enzyme could not be determined. The 2 μg. dose, which produced only a questionable hyaluronidase response on the initial clysis, had absolutely no effect on a second clysis given twenty-four hours later.

In another test, the effect of 20 μg. hyaluronidase upon the rate of administration of hypodermoclysis was quantitatively determined. Saline-dextrose solution was administered by drip clysis from a graduated fluid reservoir into the thigh by a nurse who had no knowledge of the experiment. Without enzyme, 100 c.c. of fluid was administered in forty-five minutes, and it was necessary to stop the clysis four different times for varying intervals of time to permit fluid absorption. After the subcutaneous injection of 20 μg. of hyaluronidase into the other thigh, 100 c.c. of fluid was administered in twenty-five minutes, and it was not necessary to either slow or stop the clysis. As in the previous clysis with hyaluronidase, the injected areas were soft, spread easily, and the fluid was absorbed more rapidly as compared to the area injected with fluid without enzyme. Thus with hyaluronidase the rate of fluid administration was increased approximately twofold. However, as had been previously mentioned, the extremities of this subject were very poorly developed and the connective tissues loose. Thus, the fluid ran in easily without hyaluronidase, a circumstance which has been previously pointed as tending to decrease the effect of hyaluronidase in this reaction.

During the course of the month, during which four hyaluronidase clyses were performed, a total of 2.022 mg. of hyaluronidase was administered, no significant change due to the enzyme was observed upon the red blood count, white blood count and differential, hemoglobin, or the color index. The temperature remained unaffected. No local reactions of any type developed with any of the enzyme dosages employed, and no untoward results were noted. It was of special interest that the infected decubitus ulcers on the head were in no way affected by the hyaluronidase clysis administered either in the shoulders or the thighs. Finally, the patient died a noninfectious, hydrocephalic death, ascribed to inanition.

This case demonstrates that hyaluronidase clysis administered in an area distant from localized infection does not lead to spreading of the infection. Further from this study it appears that the order of magnitude of the optimal dosage of hyaluronidase is about 20 μg., since increasing the dosage 100 times did not appear to produce a significantly greater response, and decreasing the dose to 2 μg. produced only a questionable effect. In view of the results shown in Table II, wherein 2,220 μg. of the enzyme preparation failed to be antigenic, it may be inferred that the administration of 20 μg. of bovine testis hyaluronidase should not lead to hypersensitivity in patients treated with hyaluronidase clysis.

Effect of Hyaluronidase in Hypodermoclysis in Patients.—Thereafter, hyaluronidase was utilized successfully in two additional patients.

CASE 2.—A 9-month-old white male was admitted to the hospital with a diagnosis of infectious diarrhea. The patient was severely dehydrated and M/6 sodium lactate clysis was ordered. Using the usual technique for drip hypodermoclysis, without hyaluronidase only 75 c.c. could be run into the thigh of one leg in four hours. In the other thigh, 20 μg. of hyaluronidase was injected subcutaneously in a volume of 1 c.c. Immediately thereafter, the syringe was withdrawn, leaving the needle in place, and the needle was then attached to the clysis outfit. In the presence of hyaluronidase, 150 c.c. were administered in sixty minutes. The following day clysis was repeated, and although no measurements were taken, it was observed that the thigh which received hyaluronidase twenty-four hours previously, still showed a hyaluronidase effect in that the fluid ran in quickly, and injected area was soft, and the fluid was rapidly spread and absorbed. Following treatment with sulfaguanidine, penicillin, and fluids, the patient made an uneventful recovery, and was discharged.

CASE 3.—A 9-month-old obese white male was admitted to the hospital with a temperature of 103° F. at 10:22 P.M. The patient had five convulsions lasting from one to twenty-five minutes prior to admission. Physical findings were negative except for hyperpnea and slight cyanosis of the lips. He was sedated with phenobarbital and chloryl hydrate, and there were no further convulsions. Treatment with penicillin was instituted (20,000 Oxford units intramuscularly every three hours). Drip hypodermoclysis of saline-dextrose solution, administered in the usual way without hyaluronidase, was instituted into the two thighs, but only 50 c.c. could be administered in a two-hour period. Hard lumps were noted at the injection site, and it did not appear that the injected fluid was absorbed. The patient failed during the next six hours so that at 4:30 A.M. he was in extremis, semicomatose, with a temperature of 106° F.; the pulse was feeble, the heart beat was hardly detectable, and there was peripheral circulatory collapse with generalized cyanosis. In an attempt to administer fluid intravenously, a "cut down" was performed but failed because of the patient's obesity and the peripheral vascular collapse. At 6 A.M., with the patient approaching death, 10 μg. of hyaluronidase was injected subcutaneously into each thigh, and leaving the needles in place, drip hypodermoclysis was instituted. Within fifty-five minutes, 400 c.c. of saline-dextrose was administered into the thighs. The injected areas were soft, spreading was diffuse, and the fluid was readily absorbed within thirty minutes. Thereafter, treatment with aqueous adrenal cortical extract (Upjohn) was initiated. Initially the dose was 1 c.c., administered subcutaneously every hour. After two hours, the dosage was increased to 1 c.c. per thirty minutes, and then after two more hours, the dose was increased to 2 c.c. every thirty minutes.

Within four hours after the completion of the 400 c.c. clysis, the peripheral circulation of the patient was much improved, as evidenced by disappearance of cyanosis, an increase in skin temperature and pulse. At 11:30 A.M., despite the circulatory improvement, the patient was still semicomatose. At 6 P.M. the patient was comatose but exhibited further circulatory improvement over his condition at 11:30 A.M. At this time, petechia of the pelvis and groins were observed in association with ecchymotic spots on the left knee and a clinical diagnosis of meningococcus infection with hemorrhage in the adrenals was made. 300 c.c. of saline-dextrose solution containing 5 Gm. sodium sulfadiazine was then administered by drip clysis into the areas previously treated with hyaluronidase. This clysis was completed within two hours. Again the injected areas were soft, spreading was diffuse, and the absorption of the fluid was rapid. Treatment with adrenal cortical extract and penicillin was continued. Although the peripheral circulation was well maintained, the patient remained comatose and at 2 A.M. of the next morning the child expired. Post-mortem examination confirmed the clinical diagnosis, and there was no evidence that the hyaluronidase produced a toxic reaction or contributed to the death of the patient.

DISCUSSION

The enzyme, hyaluronidase, possesses a variety of biologic activities and has been related to numerous processes ranging from bacterial invasiveness to fertilization of the mammalian ovum.[3] Thus, hyaluronidase not only produces the spreading reaction, but in addition has the activity to (a) decapsulate certain strains of streptococci,[9] (b) remove the cumulus cells surrounding the ovum of the rabbit,[10, 11] and (c) decrease the viscosity of synovial fluid.[5] Attempts to utilize hyaluronidase clinically have been initiated but as yet have not been fully explored. Thus, injection of hyaluronidase into pathologic joints wherein the viscosity of the exudate appeared to be increased, lowered the viscosity of the exudate without permanently improving the pathologic condition.[12] Hyaluronidase has been successfully used for paracentesis in a case

of mesenthelioma of the pleura and peritoneum to facilitate the removal of a fluid of honeylike consistency.[5] It has been asserted that hyaluronidase was successfully used to induce pregnancy in certain cases of sterility.[13] The details of this work have been published in *The American Journal of Medicine* **1**: 491, 1946.

In this study, the spreading activity of hyaluronidase has been successfully utilized to facilitate clinical hypodermoclysis. The results demonstrate that microgram amounts of a preparation of hyaluronidase facilitate the administration and absorption of subcutaneously administered fluid in both man and experimental animals. This effect of hyaluronidase seems to be dependent upon the state of the subcutaneous connective tissues. Thus when the connective tissues are loosely organized, as was the case in rabbits and our hydrocephalic patient, hyaluronidase increased the rate of administration about twofold. In guinea pigs and two patients where the subcutaneous connective tissues were well developed, the rate of fluid administration was increased to a much greater extent by the subcutaneous administration of hyaluronidase prior to clysis. While quantitative evaluation of the effects of hyaluronidase to increase circulatory absorption was not possible, an indirect, qualitative method, based upon the disappearance of the localized swelling produced by the injection of large volumes of fluid, clearly demonstrated that the enzyme promoted absorption. Thus, the swellings produced by clinical hypodermoclysis in enzyme-treated areas disappeared within ten to twenty minutes after cessation of injection, while in the absence of hyaluronidase sixty to ninety minutes were required. Inasmuch as the clinical trials of hyaluronidase were in infants, no information concerning the effect of enzyme in reducing the pain of hypodermoclysis was obtainable. While the patients appeared to be less troubled by clysis in hyaluronidase-treated areas, direct evidence that hyaluronidase prevents pain due to distention produced by fluid administration was obtained in our studies with normal adults who received an intradermal injection of 1.0 c.c. saline, with and without hyaluronidase. Without enzyme, this volume of fluid introduced intracutaneously produced intense pain which persisted for ten to fifteen minutes, while the same volume administered with hyaluronidase produced no pain at all. Further work with older children and with adults will be necessary to determine whether the pain resulting from distention produced by clysis is completely or only partially removed by hyaluronidase. Our studies demonstrate that the administration of 0.2 to 2.2 mg. of hyaluronidase to human volunteers, or 10 to 100 times the dosage required for clysis, failed to induce hypersensitivity in seven adult human beings. Thus, the effect of hyaluronidase in facilitating clinical hypodermoclysis is obtained with such small doses of enzyme extract (approximately 10 to 20 μg.) that no hypersensitivity to testis protein results, although the enzyme preparation available to us is antigenic in guinea pigs. While admittedly it would be clinically desirable to have available a non-antigenic hyaluronidase preparation, this possibility remains for further biochemical investigation. In the meantime, the enzyme in its present degree of purity would appear to be suitable for further clinical trial.

Since hyaluronidase promotes spreading of bacteria, as well as the fluids used in clysis, the finding that hyaluronidase clysis in one of our patients did not enhance a pre-existing localized infection at a site distant from the injected area is important, since it demonstrates that the presence of a localized infection does not contraindicate the use of enzyme as an aid in clysis. This clinical result confirms the previous findings of Sannella[7] who demonstrated that hyaluronidase-saline clysis failed to enhance an experimentally induced *Staphylococcus aureus* infection in rabbits. An explanation for the failure of a hyaluronidase clysis to affect a localized infection is afforded by the finding that hyaluronidase injected into normal skin diffuses around, but not through, an area of skin containing a fibrin barrier.[14] This result, taken together with the finding that hyaluronidase injected directly into an area containing fibrin can penetrate the barrier, demonstrates that enzyme injected into normal skin diffuses in a path of least resistance and consequently does not pass through an area of skin containing a fibrin barrier. Since the localization of bacteria is due in large part to fibrin deposition in the lymphatics and the interstitial spaces in infected skin,[15] an explanation for the absence of any hyaluronidase effect upon a pre-existing localized infection is evident.

While this report has dealt with the usefulness of hyaluronidase in facilitating the subcutaneous administration of large volumes of salt solutions (with and without glucose), hyaluronidase may also be useful for the subcutaneous administration of large amounts of plasma and drugs. We have found that in newborn infants the swellings produced by the subcutaneous injections of 30 c.c. amounts of plasma with hyaluronidase disappear within sixty minutes; without enzyme, six to twenty-four hours are required before the swellings disappear. While as stated previously, it is not possible to deduce accurately from this type of data the rate of circulatory absorption of the subcutaneously administered plasma, it seems clear that plasma absorption is likewise facilitated by hyaluronidase. This finding may be of some importance in those clinical conditions such as infectious diarrhea, where plasma must be administered, and where recourse to the intravenous route is difficult.

SUMMARY

1. Microgram amounts of a bovine testis hyaluronidase preparation markedly facilitates the administration of hypodermoclysis in experimental animals.

2. The administration to human volunteers of milligram amounts of the hyaluronidase preparation produces no toxic reactions aside from a nonspecific transient foreign protein reaction. These reactions do not occur when the dosage is decreased to 200 μg.

3. Milligram doses of enzyme did not produce hypersensitivity to bovine testis proteins in the volunteer subjects, although the preparation in larger doses is antigenic in guinea pigs.

4. In three patients, hyaluronidase administered subcutaneously in a dosage of 10 to 20 μg. markedly increased the rates of absorption and administration of hypodermoclysis with no untoward reactions.

5. In one patient, the administration of hyaluronidase clysis did not influence a pre-existing localized infection.

6. In another patient with circulatory collapse, the circulation was restored successfully after ordinary hypodermoclysis and an attempted "cut down" for intravenous administration failed.

7. It is suggested that hyaluronidase deserves further clinical trial and study as an aid in hypodermoclysis.

REFERENCES

1. Duran-Reynals, F.: J. Exper. Med. **50**: 327, 1929.
2. McClean, D.: J. Path. Bact. **33**: 1045, 1930.
3. Duran-Reynals, F.: Bact. Rev. **6**: 197, 1942.
4. Mann, T., and Lutwak-Mann, C.: Ann. Rev. Biochem. **13**: 25, 1944.
5. Meyer, K.: In Green, D. E. Currents in Biochemical Research, New York, 1946, Interscience Publishers, pp. 284-288.
6. Hechter, O.: J. Exper. Med. **85**: 77, 1947.
7. Sannella, L. S.: Yale J. Biol. Med. **12**: 433, 1940.
8. Madinaveitia, J.: Biochem. J. **35**: 447, 1941.
8a. Kass, E. H., and Seastone, C. V.: J. Exper. Med. **79**: 319, 1944.
9. McClean, D.: J. Path. Bact. **53**: 156, 1941.
10. McClean, D., and Rowlands, J. W.: Nature **150**: 627, 1942.
11. Fekete, E., and Duran-Reynals, F.: Proc. Soc. Exper. Biol. & Med. **52**: 119, 1943.
12. Ragan, C., and DeLamater, A.: Proc. Soc. Exper. Biol. & Med. **50**: 349, 1942.
13. Leonard, S. L., and Kurzrock, R.: Endocrinology **37**: 171, 1945.
14. Hechter, O.: Unpublished work.
15. Menkin, V.: Dynamics of Inflammation; an Inquiry into the Mechanism of Infectious Processes, New York, 1940, The Macmillan Company.

LUNG CALCIFICATIONS AND HISTOPLASMIN-TUBERCULIN SKIN SENSITIVITY

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RECENT studies have demonstrated a relationship between histoplasmin skin sensitivity and lung calcification. As a part of the Fels Research Institute's longitudinal study of 200 normal southwestern Ohio children, chest x-rays and skin sensitivity tests have been done. Because of the serial nature of this research program, which includes these yearly chest x-rays from birth, certain of the data seem peculiarly suited to a study of the relationships of histoplasmin skin sensitivity to lung calcification and other factors.

In the past ten or fifteen years there has been an increasing interest in the etiology of pulmonary calcification. There have been many reports in the literature concerning the discrepancy between tuberculin-positive skin reactions and the presence of pulmonary calcifications. It has been shown[1-3] that from 27 to 83 per cent of young individuals, living for the most part in or adjacent to the eastern slope of the Mississippi River basin and the bordering states of the western slope, have demonstrable pulmonary calcification previously accepted by most roentgenologists as indicative of healed primary tuberculosis. Yet, less than one-half of the individuals with lung calcifications were found to have positive tuberculin reactions.

Thus, the classification of the significance of lung calcifications has remained a challenge to investigators. Several years ago, Cox and Smith[4] and Aronson and associates[5] showed that coccidioidomycosis could produce pulmonary lesions which calcify and produce x-ray findings identical with those of primary pulmonary tuberculosis. However, the occurrence of coccidioidomycosis seems to be limited for the most part to certain areas of the west. Christie and Peterson[1-3] and Palmer[6] have shown that there is a high correlation between positive histoplasmin cutaneous sensitivity reactions and the presence of pulmonary calcifications in individuals who do not react to tuberculin. These findings are in accordance with the suggestion of Smith[7] that histoplasmosis occurs most frequently in those areas in which the incidence of pulmonary calcification with negative tuberculin reactions is high. They have suggested that apparently a nonfatal form of histoplasmosis does occur and can produce intrathoracic calcifications. They have further shown that in their series the incidence of positive histoplasmin reactions far outnumbers the incidence of positive tuberculin reactions in individuals with pulmonary calcifications. Observations by these investigators have also shown that some individuals with pulmonary calcifications react neither to tuberculin nor to histoplasmin. The purpose of this paper is to present further observations pertinent to the problem

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of lung calcification. Along with incidence of lung calcifications and positive tuberculin and histoplasmin skin reactions, it will deal with such questions as: (1) age of appearance of lung calcification; (2) age of appearance of lesion preceding calcification; (3) age difference in positive histoplasmin and tuberculin skin reactions, and the progressive changes in patterns of precalcification lesions and calcification.

TABLE I. FELS CHILDREN BY AGE GROUP SHOWING REACTIONS TO TUBERCULIN AND HISTOPLASMIN

AGE WHEN TESTED* (YR.)	NO. IN GROUP	TUBERCULIN-POSITIVE		HISTOPLASMIN-POSITIVE		TUBERCULIN-POSITIVE AND HISTOPLASMIN-POSITIVE		TUBERCULIN-NEGATIVE AND HISTOPLASMIN-NEGATIVE	
		NO.	%	NO.	%	NO.	%	NO.	%
Under 5	45	3	6.7	5	11.1	1	2.2	38	84.4
5-9	53	1	1.9	25	47.1	0	0	27	52.9
10-14	50	13	26.0	32	64.0	11	22.0	16	34.0
15-19	22	9	40.9	14	63.6	6	27.2	5	22.7
Total	170	26	15.3	76	44.7	18	10.5	86	51.1

*No children less than one year of age were tested, and those whose parents refused skin tests were omitted from the study.

STUDY GROUP AND MATERIALS

The children who are studied at the Fels Research Institute are so-called "normal children." Since almost all of them have been admitted to the study prior to birth, they obviously are unselected with regard to such factors as health and growth progress. The children and their families live in cities, small towns, and rural areas. While the "Fels population" is higher than both the national average and the Ohio average in economic status, the group includes, nevertheless, children from all economic levels and from all types of homes. The age distribution is shown in Table I.

TABLE II. THE OCCURRENCE OF SENSITIVITY TO TUBERCULIN AND HISTOPLASMIN, AND THE PRESENCE OF INTRATHORACIC CALCIFICATIONS IN FELS CHILDREN

NO. EXAMINED	TUBERCULIN-POSITIVE		HISTOPLASMIN-POSITIVE		NO. SHOWING INTRATHORACIC CALCIFICATIONS	
	NO.	%	NO.	%	NO.	%
170	26	15.3	76	44.7	103	60.6

Because of the longitudinal principle of the study, serial chest x-rays have been taken on most children at 1, 6, 12, 18, and 24 months, and at yearly intervals thereafter. On some of the children the early x-rays were taken at 1, 4, 10½, 16½, and 22 months. The films are chest-size, taken at 6 feet. The serial nature of these x-rays makes possible not only a diagnosis of presence or absence of lung calcification but also a study of the progressive changes in the lung from the time of the initial lesion through the period of calcification. Often we have come to recognize the true nature of the initial lesion only when the soft tissue changes began to be supplanted by calcification. Thus, a lung marking which in a 4-month x-ray was taken for a blood vessel, may have become at 10½

months a definite spot of consolidation, and by 22 months may have begun to calcify. The serial x-rays have made it possible, therefore, to observe the nature of the initial lesion, its progress and period of existence before calcification, and to learn as well of any progressive calcification in later years or of any resorption of existing calcification.

Single x-rays of the chests of both parents have been taken, and since there are as many as seven siblings in a family, almost all of whom have been serially x-rayed and skin tested, sibling incidence of histoplasmin reactions may also be studied. Physical examinations at six-month intervals since birth, as well as continuous illness records, constitute part of the material.

All children included in the study were given first strength (.00002 mg.) Purified Protein Derivative intradermally on one arm and histoplasmin, $\frac{1}{10}$ c.c. of 1:1,000 on the other. These reactions were read in seventy-two hours. If the tuberculin was negative, the second strength (.005 mg.) was given. If both strengths of tuberculin and the histoplasmin gave negative tests, and if pulmonary calcifications were present, the child was tested with $\frac{1}{10}$ c.c. of 1:1,000 extract of *Haplosporangium parvum* and the same quantity of blastomycin, an extract of the fungus *Blastomyces dermatides*.* While the x-rays of these children were taken at frequent intervals from birth on, all of the skin tests, the results of which are shown in accompanying tables, were done during the year 1946. Many additional tuberculin skin tests were done on most of these children earlier, particularly on those having heavy lung calcifications. In no instance has a tuberculin skin test found positive at one application become negative at a later one. Perhaps by chance, all of those children with heavily calcified areas and negative tuberculin tests at an early age have, in every instance, continued to have negative tests.

RESULTS AND DISCUSSION

One hundred and seventy children, all one year of age or older, were tested with tuberculin and histoplasmin. Twenty-six (15.3 per cent) reacted to either .00002 or .005 mg. of Purified Protein Derivative. Seventy-six (44.7 per cent) reacted to histoplasmin, 1:1,000. One hundred and three (60.6 per cent) children had demonstrable pulmonary calcifications. These results are shown in Table II. They demonstrate the greater incidence of sensitivity to histoplasmin than to tuberculin. These findings are in accord with the results of similar series reported by others,[1, 2, 5] and emphasize the fact that many more calcifications occur in tuberculin nonreactors than in tuberculin reactors.

In Table I the age distribution of the children in relation to their reactions is shown. These results show an increase in positive tuberculin reactions until a maximum of 40.9 per cent in the 15- to 19-year age group is reached, with the exception of the 5- to 9-year period, which shows a drop (not statistically significant). The increasing incidence of pulmonary calcifications is much more

*This material and the histoplasmin were supplied by the United States Public Health service through the courtesy of Dr. Carroll E. Palmer, for whose help we are deeply indebted.

rapid and far exceeds the rate of increase in positive tuberculin reactions. This relationship is shown in Fig. 1. In the older age groups, however, the incidence of pulmonary calcification appears to flatten out, while the tuberculin reactions continue to increase. It is interesting to note that the incidence of calcifications with negative tuberculin and histoplasmin reactions changes little after the age of 5. This fact suggests that the etiology of these lesions is distinct from that of the tuberculin-histoplasmin groups, and is not merely a lag in the development of sensitivity to these agents. The graphic picture is very similar to Christie and Peterson's presentation,[3] except that the onset of the calcification exceeds the development of the histoplasmin sensitivity, in contrast to theirs,

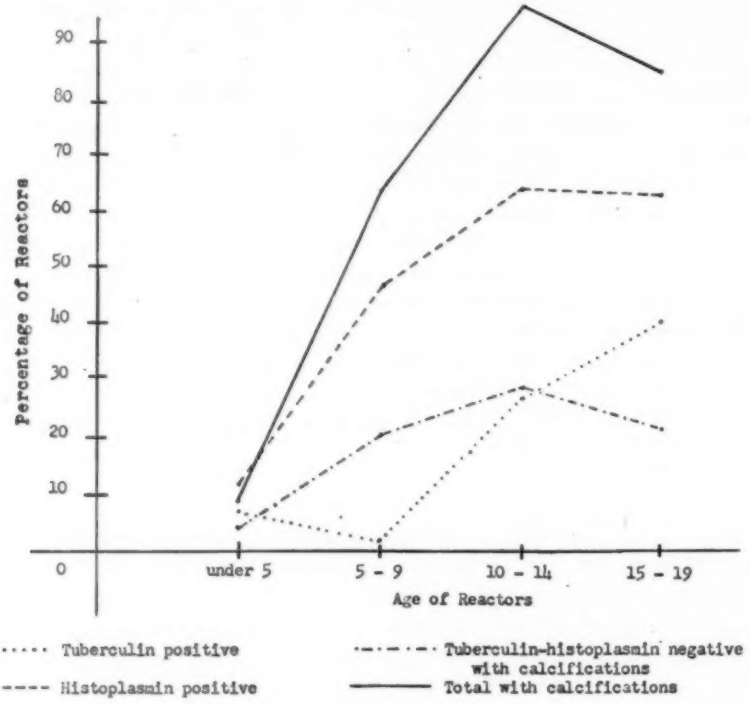


Fig. 1.

which shows a lag of calcification in relationship to histoplasmin reaction. We assume from our data either that the onset of sensitivity to histoplasmin lags behind the onset of calcification or that many calcifications are due to causes other than histoplasmosis infection. The similarity of the histoplasmin and calcification curves is striking, as is the nonsimilarity between the tuberculin and calcification curves. These same similarities and dissimilarities were emphasized by Christie and Peterson.[3]

TABLE III. FELS CHILDREN ACCORDING TO REACTION WITH TUBERCULIN AND HISTOPLASMIN AND THE PRESENCE OF INTRATHORACIC CALCIFICATION IN THESE REACTORS

TYPE OF REACTION	NO.	% WHOLE GROUP	NO. WITH CALCIFICATION	% REACTION GROUP WITH CALCIFICATION
Tuberculin + Histoplasmin +	18	10.6	15	83.3
Tuberculin + Histoplasmin -	8	4.7	6	75.0
Tuberculin - Histoplasmin +	58	34.1	49	84.4
Tuberculin - Histoplasmin -	86	50.6	33	38.3
Total	170	100.0	103	60.6

Table III shows the number and percentage of children according to the reactions to tuberculin and histoplasmin and the presence of calcifications in these reactors. A larger percentage of histoplasmin reactors have calcifications than do tuberculin reactors. As high an incidence of calcifications occurs in the group which are positive to both histoplasmin and tuberculin. Again these results are similar to those of Christie and Peterson. A larger percentage of our reactors have pulmonary calcifications than do those in their series. A part of this difference may be attributable to the greater ease and certainty of recognizing calcification from a series of plates. Often a calcification may show up on four x-ray films, but because of positioning or slight movement, may be doubtful on the fifth.

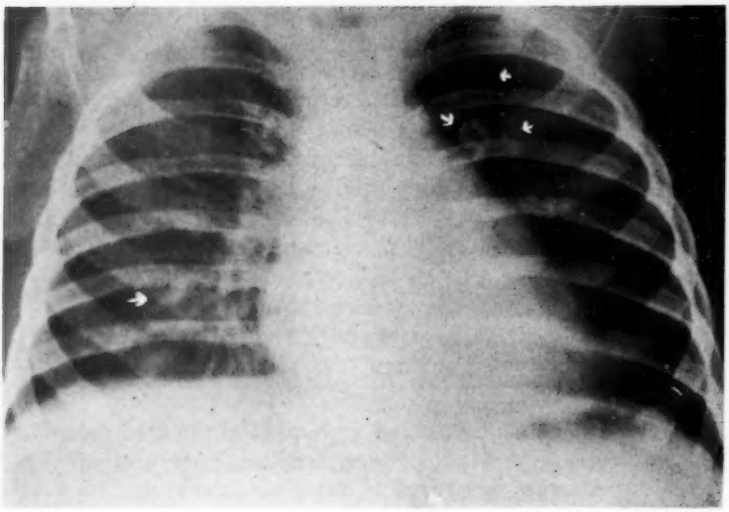
Table IV reveals the rather striking fact that thirty-three children with pulmonary calcifications reacted neither to tuberculin nor histoplasmin. Since all positive histoplasmin reactions yielded areas of induration and erythema of more than 5 mm., we feel that stronger strengths of histoplasmin probably

TABLE IV. HISTOPLASMIN AND TUBERCULIN REACTIONS IN 103 FELS CHILDREN WITH PULMONARY CALCIFICATION

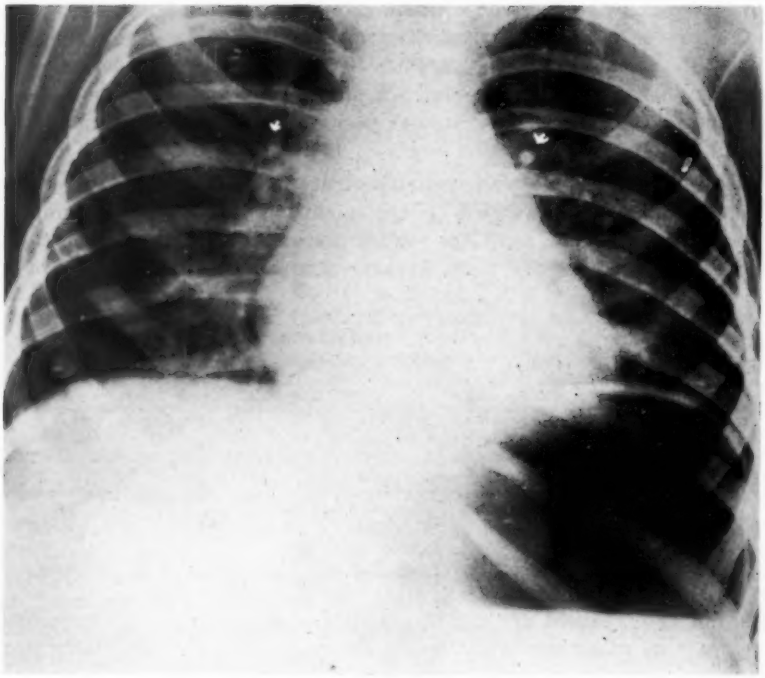
PULMONARY CALCIFICATION AND	NO. WITH CALCIFICATION		% WITH CALCIFICATION	
Histoplasmin +, Tuberculin +	15		14.5	
Histoplasmin +, Tuberculin -	49		47.5	
Subtotal Histoplasmin +		64		62.1
Tuberculin +, Histoplasmin +	15		14.5	
Tuberculin +, Histoplasmin -	6		5.8	
Subtotal Tuberculin +		21		20.3
Histoplasmin -, Tuberculin -	33		32.0	

would not have resulted in a significant number of positives. We have assumed, therefore, that other etiological agents are responsible for calcifications in this group.

Table V shows the results of testing these thirty-three children with haplosporangin and blastomycin. One of these children, a girl of 14 with prominent calcifications, reacted severely to both blastomycin and haplosporangin.

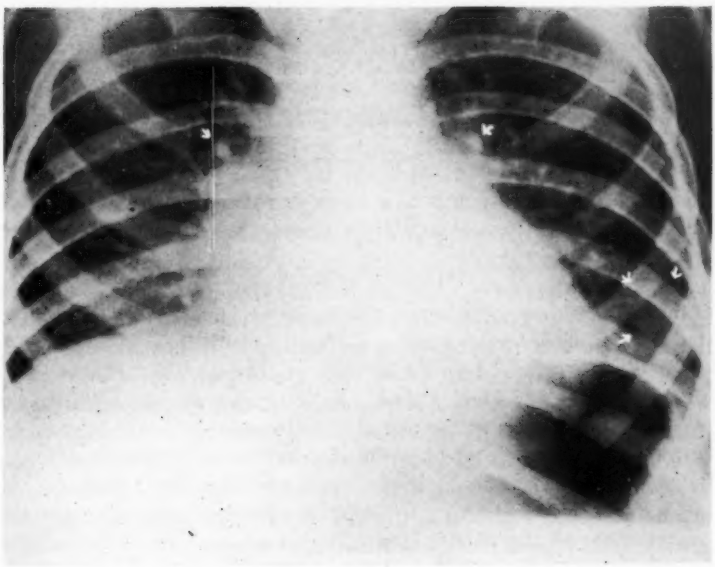


A.

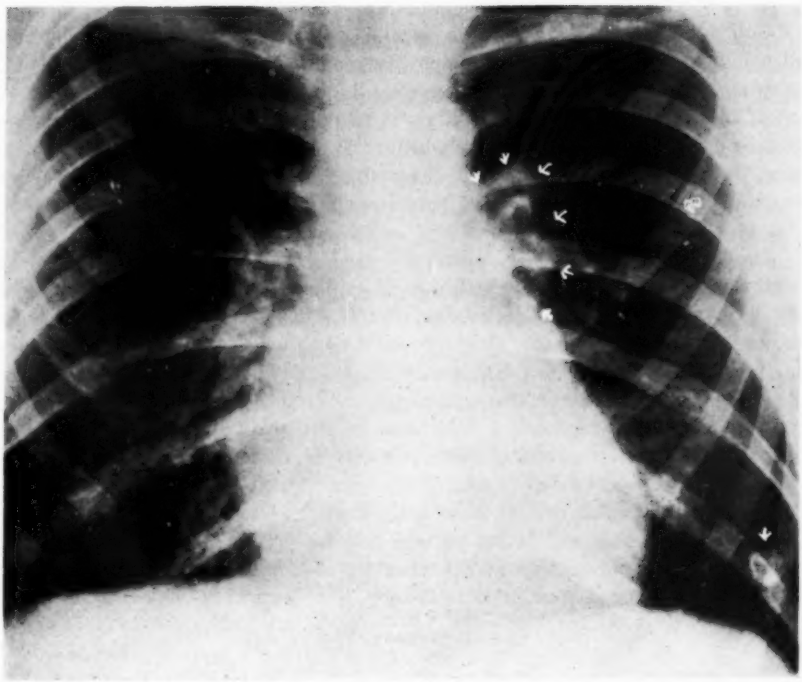


B.

Fig. 2.—The series of chest x-rays shown above pictures the changes occurring in the chest of one child from the age of 10½ months to 6½ years. *A* shows increase in markings in left hilus and apex and right base; *B*, at 22 months, shows areas of calcification in both hiluses; *C*, at 34 months, shows round area of infiltration at left base; *D*, at 6½ years, shows calcification of this area plus extensive calcification of a large hilus gland on the left, apparently resulting from drainage of the previous infiltration in the left base.



C.



D.

(For legend, see opposite page.)

TABLE V. RESULTS OF TESTING THIRTY-THREE CHILDREN WITH INTRATHORACIC CALCIFICATIONS, BUT WITH NEGATIVE TUBERCULIN AND HISTOPLASMIN REACTION TO HAPLOSPORANGIN AND BLASTOMYCIN

NO.	POSITIVE HAPLOSPORANGIN	POSITIVE BLASTOMYCIN
33	1	2

The child had what corresponds to a 4+ tuberculin reaction at the site of the tests. She likewise had tender axillary adenopathy, fever, and general malaise.

INCIDENCE IN SIBLINGS

Of the 170 children skin-tested, the majority have one or more siblings in the tested group. There are a number of families with three siblings, a few with four, and one with six children whose tests and x-rays constitute a part of our research data. It is, therefore, possible to determine whether siblings show the same reactions, either positive or negative, with greater incidence than is found in the group in general, either in terms of skin tests or calcification.

Histoplasmin Tests.—By pairing every sibling against each of his other siblings (108 pairs), we find that in 34 per cent of the cases when one sibling is negative the other of the pair is also. This is against an unselected group expectancy of 31 per cent. Of those pairs in which one is positive, 23 per cent showed both positive, against an unselected group expectancy of 20 per cent. By the method of Chi Square, these differences are not statistically significant.

Calcifications.—When one of a pair of siblings had calcification, the other had calcification in 43 per cent of the cases, against a normal expectancy of 37 per cent. When one sibling was negative, the other was also negative in 22 per cent of the cases, against an expectancy of 15 per cent. Both of these figures are statistically significant, with a probability of .02, or 2 chances in 100, that the difference is accidental. Since the histoplasmin shows no familial factor and the calcification does, its familial factor must be the result of tuberculosis and other cross-infectious conditions.

Previous to the currently accumulating knowledge of the prevalence and distribution of positive skin reactors to histoplasmin, histoplasmosis was known only as a fairly rapidly progressing, nearly always fatal disease. This fact has constituted a part of the basis for doubt as to whether positive histoplasmin skin reactors, who were not apparently ill, actually had been or were infected with the organism *Histoplasma capsulatum*. While none of the children in our group presented any symptom syndrome in any way comparable to those reported for proved acute cases of histoplasmosis, we do believe that it is premature to say that all of our cases are completely asymptomatic. There is a strong suggestion from the serial growth data and illness histories of these children that their growth progress and health pattern may be significantly different from the negative histoplasmin reactors. An analysis of any such differences will form the basis for a future paper.

X-RAY INTERPRETATION

The serial nature of our chest x-rays permits us to study the development of pulmonary calcifications from the precalcification or infiltrative stage to the

completely calcified lesion. As previously stated, we are able to distinguish much more clearly between false calcifications, i.e., bronchi and blood vessels on section, and artifacts, by studying the serial plates, than would have been possible had only one roentgenogram been made. Progress of the lesion, increases in density, and elimination of difficulties due to position or slight motion, all added to accuracy of determination of calcification.

Parenchymal lesions occurred much more frequently in the bases than in the apices, although they did occur in both. Initial lesions varied from fuzzy, fan-shaped extensions and exaggerations of linear markings into the periphery, to round areas of definite consolidation, often 2.5 cm. or more in diameter. Such lesions show beginning calcification twelve to fifteen months later and are heavily calcified in two or three years. Calcification of hilus glands draining such initial lesions often does not occur until two and one-half or more years later. Fig. 2 shows an interesting sequence of the progress of the lung lesions in a child strongly positive to histoplasmin but repeatedly negative to tuberculin. His 4-month x-ray (not shown) suggested a flocculent exaggeration of lung markings into the peripheries from both lung roots. From this single x-ray one could not be sure that the lung markings were abnormal. There was no hilus calcification at this time. His 10½-month x-ray (Fig. 2, *A*) showed quite clearly this flocculent picture extending out from the lung roots. There was a suggestion of beginning calcification in the left hilus at 16½ months. At 22 months (Fig. 2, *B*) there was definite calcification of the suspected area in the left hilus and an equally dense calcification in the right hilus. At 34 months (Fig. 2, *C*) there was a pneumonic patch of consolidation, 2 cm. in diameter, in the left base at the costophrenic angle. At 45 months this area was just beginning to calcify. At 57 months the calcification was increasingly dense but not so dense as it was at 6½ years and not nearly so dense as at 8½ years. At 6½ years (Fig. 2, *D*) there was first seen the beginning calcification of a large hilus gland on the left, a condition which had progressed markedly by the age of 7½ years. This large area of calcification seemed to be the result of drainage from the earlier area of pneumonic consolidation in the left base. The calcification in the left base, which was quite dense, was much smaller than the original consolidation.

This sequence of events, repeated with variations in the series of x-rays of other children, has a number of interesting implications; some of these are:

1. That the infection producing the calcification often occurs at a very early age. In our series there are nine cases in which the soft tissue changes are present at 10½ months of age. Thirty were present before the age of 24 months. Age of onset is shown in Table VI.

2. That there is a considerable lag between the initial soft tissue lesion in the parenchyma and calcification.

3. That there is often a lag of two years or more between a soft tissue lesion and a hilus calcification.

4. That the process is often a progressive one, showing new soft tissue lesions and additional areas of both parenchymal and hilus calcification over

TABLE VI. AGE AT ONSET OF PULMONARY LESION RESULTING IN PULMONARY CALCIFICATION

RESULT	NO. REACTORS	NO. CALCIFICATIONS	AGE ONSET LESION (MO.)				AGE ONSET CALCIFICATION (MO.)			
			0-24	25-48	49-72	OVER 72	0-24	25-48	49-72	OVER 72
Histoplasmin + Tuberculin +	18	15	4	5	4	3	0	6	3	6
Histoplasmin + Tuberculin -	58	49	10	24	10	4	4	15	18	12
Histoplasmin - Tuberculin +	8	6	3	2	1	0	2	1	3	0
Histoplasmin - Tuberculin -	86	33	13	13	4	3	3	14	10	6
Total	170	103	30	44	19	10	9	36	34	24

a period of six or more years. There are many such progressive cases in our group.

5. That calcification itself often appears very early. Of the 103 cases showing calcification, it was apparent and verifiable from later x-rays in nine cases in the first 24 months of life. In forty-five it was present at or before the 48-month x-ray.

This early calcification is in sharp contrast to the findings of Christie and Peterson, the difference probably being due to the group and perhaps partially to an increased facility of recognition by reason of our serial plates.

We attempted from our study of the serial x-rays to establish some criteria which would allow us to distinguish between the calcification patterns of the positive histoplasmin and tuberculin reactors. We were unable to do so, since identical patterns could be found in individuals who reacted to tuberculin, histoplasmin, or neither. There was, however, a tendency for calcifications associated with positive histoplasmin reactions to be: (1) multiple in the parenchyma, often with calcifications present in upper lung fields and apices; (2) early in onset, frequently with the initial lesion appearing before one year of age, the majority before 4 years of age; (3) preceded occasionally by a pneumonic infiltrate early in the infection; (4) progressive with the development of new lesions and calcifications over a period of years (eighteen of the forty-nine calcifications of the histoplasmin positive group were of this nature).

SUMMARY

We have presented the results of our investigations of the serial chest x-rays and histoplasmin-tuberculin sensitivity reactions in 170 essentially "normal" southwestern Ohio children. On thirty-three children with positive calcification and negative skin reactions, we have applied haplosporangin and blastomycin skin tests. We have re-emphasized the findings of other investigators that a far greater number of children are sensitive to histoplasmin than to tuberculin, and that the incidence of pulmonary calcification is much more closely associated with the incidence of histoplasmin sensitivity than with tuberculin sensitivity. There is a much closer association between the onset

of the calcification and the development of histoplasmin sensitivity than between calcification and the development of tuberculin sensitivity. A considerable number of calcifications occur in children negative to both histoplasmin and tuberculin. One of these was associated with a positive blastomycin test and one with positive haplosporangin plus a positive blastomycin test. In our series there is a tendency for familial distribution of positive lung calcifications, but not of positive histoplasmin skin reactions.

The majority of the calcifications in our study have their soft tissue changes before 48 months of age. Many of these can be traced back to the early months of life. Infiltrates and occasional round areas of consolidation are the precursors of the calcifications in the parenchyma. Progressively appearing new lesions followed by new calcifications both in parenchyma and hilus are often seen in histoplasmin-positive children over a period of several years.

CONCLUSIONS

1. A study of serial chest x-rays and cutaneous sensitivity to histoplasmin and tuberculin re-emphasizes the close relationship between histoplasmin reactors and pulmonary calcifications in children.

2. The onset of infections producing lung calcifications in our group is very early.

3. *Blastomyces dermatides* and *Haplosporangium parvum* may play a minor role in the etiology of pulmonary calcifications in this area.

4. Pulmonary calcifications are apparently nonspecific reactions to a variety of organisms. Cutaneous sensitivity tests and procedures other than roentgenologic must be employed to make an etiological diagnosis.

5. Pulmonary calcification in positive histoplasmin reactors is not infrequently continuous over a period of six or seven years, with new precalcarious and calcarious lesions appearing after months or years. This radiologic picture suggests that the activity of the histoplasmin organism in the body may remain active for very long periods.

REFERENCES

1. Christie, Amos, and Peterson, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, Am. J. Pub. Health **35**: 1131, 1945.
2. Christie, Amos, and Peterson, J. C.: The Relationship of Sensitivity of Histoplasmin, Tuberculin, and Haplosporangin to Pulmonary Calcification, J. A. M. A. **131**: 658, 1946.
3. Christie, Amos, and Peterson, J. C.: Histoplasmin Sensitivity, J. PEDIAT. **29**: 417, 1946.
4. Cox, Alvin J., and Smith, Charles Edward: Arrested Pulmonary Coccidioidal Granuloma, Arch. Path. **27**: 717, 1939.
5. Aronson, Joseph D., Saylor, Robert M., and Parr, Erma L.: Relationship of Coccidiomycosis to Calcified Pulmonary Nodules, Arch. Path. **34**: 31, 1942.
6. Palmer, Carroll E.: Non-tubercular Pulmonary Calcifications and Sensitivity to Histoplasmin, Public Health Report 60, 513, 1945.
7. Smith, Charles E.: Coccidiodomycosis, M. Clin. North America **27**: 790, 1943.

CEPHALIN-CHOLESTEROL FLOCCULATION IN PREMATURE INFANTS AND CHILDREN RECEIVING IMMUNE GLOBULIN

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SINCE Hanger[1] first described the cephalin-cholesterol flocculation for aid in diagnosis of liver disorders, its use for this purpose has become extensive. There are, however, many factors which may influence the test, producing positive results. Exposing the mixed material to light,[2] marked changes in temperature, including refrigeration of the serum,[3] failure to prepare fresh cephalin-cholesterol solution, and the presence of traces of heavy metal or strong acids, will give erroneous flocculation. In pediatric practice, we are confronted with at least two other examples of a positive test being obtained where no liver damage has been found. The first and most common example is in reference to the serum of the newborn. Salmon and Richman[5] demonstrated that the flocculation was positive in all newborn infants studied, and remained so during the first week. These workers found that the mother's serum also gave positive results during this same period. There was no relation to icterus or general condition of these infants, and the reaction became negative at approximately the same time in each. All the reported infants were full term and weighed above 2,500 Gm.

It was decided to try the flocculation on the blood of a limited number of premature babies. Blood for the experiment was obtained from the external jugular vein. The test was performed as described by Hanger, using 0.2 c.c. of a cephalin-cholesterol emulsion. This emulsion was prepared from a cephalin-cholesterol mixture dispensed by Wilson Laboratories, Chicago, Ill. The mixture contains 100 mg. of partially oxidized cephalin and 300 mg. of cholesterol. It was dissolved in 8 c.c. of anesthesia ether and 1 c.c. of the ether solution was added to 35 c.c. of distilled water. The aqueous emulsion then was allowed to simmer below boiling until a final volume of 30 c.c. was reached. This emulsion was brought to room temperature before using and was prepared on the day the tests were performed. After adding 1 c.c. of the emulsion to the diluted serum, the solution was placed in a dark place at room temperature and flocculation was noted in twenty-four and forty-eight hours. One plus to 4+ reactions were recorded, depending on how clear the supernatant fluid appeared. A 4+ reaction was recorded when all the cephalin-cholesterol had settled to the bottom of the tube.

The results, which were rather inconsistent, are shown in Table I. All the sera from these premature infants gave positive tests shortly after birth, but the duration of the reaction varied. As was also noted by Salmon and Richman,[5] there appeared to be little correlation to jaundice or to the general condition of the patient. The triplets (patients 1, 2, and 3) gave similar reactions during the time all were living. The two that survived became negative

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TABLE I. CEPHALIN-CHOLESTEROL FLOCCULATION IN PREMATURE INFANTS

PATIENT	AGE	WEIGHT (GM.)	ICTERUS	CEPHALIN FLOCCULATION 24 HR.	CEPHALIN FLOCCULATION 48 HR.	COMMENT
1.	30 hr.	1,260	0	±	+++	
	6 days	1,440	0	+	+++	
	13 days	1,463	+	0	±	One of triplets
2.	30 hr.	1,305	0	+	+++	
	6 days	1,215	0	+	+++	
	13 days	1,100	+	0	0	One of triplets
3.	30 hr.	1,500	0	+	+++	A triplet, died third day
4.	12 hr.	1,620	0	++	+++	
	6 days	1,440	+	++	+++	
	11 days	1,575	0	0	+	
	15 days	1,688	0	0	0	
5.	2 days	2,340	0	++	++++	
	7 days	2,205	+	++	+++	Died at eight days
6.	2 days	1,013	0	++	++++	
	6 days	945	++	++	++++	
	10 days	945	++	0	0	
7.	2 days	1,660	0	0	++	
	7 days	1,635	++	0	++	
	11 days	1,635	++	0	++	
	16 days	1,744	+	0	0	
8.	2 days	1,688	0	+	+++	Diarrhea present
	11 days	1,603	+	0	+++	Plasma given intravenously
	15 days	1,603	0	0	+++	
	19 days	1,631	0	+	+++	

at about the same time. Only one premature infant (patient 8) had a positive test after the second week, and this patient received several injections of human plasma for treatment of diarrhea.

Moore and associates[6] stated that in disease, a positive flocculation may be obtained with a serum due to any of the following alterations: (1) increase of gamma globulin in such quantity that there is insufficiency of the normal components of the serum albumin fraction to inhibit the reaction; (2) diminution of the serum albumin fraction below initial levels necessary to inhibit the reaction; (3) diminution in the flocculation inhibiting properties of the albumin fraction. There are many alterations in the newborn infant's blood which are peculiar to this period of life, and one of these is the high titer of antibodies carried over from the maternal circulation. Since the gamma globulin fraction represents some of these antibodies, the globulin fraction is increased. Whether this is adequate to explain the positive flocculation can be proved only by accurate determination of the gamma globulin and albumin in the infant at the time the flocculation is performed. This also should be obtained in the mother, since it has been found that her flocculation is positive during the same period of time as that of the infant.

As suggested above, gamma globulin and albumin fractions present in the patient's serum probably influence the degree of flocculation. The gamma globulin appears to produce positive results, while the albumin has an inhibitory effect. Recently, gamma globulin for the prevention of measles has become

TABLE II. CEPHALIN-CHOLESTEROL FLOCCULATION AFTER GAMMA GLOBULIN

PATIENT	AGE (YR.)	WEIGHT (KG.)	DIAGNOSIS	CEPHALIN FLOCCULATION BEFORE GAMMA GLOBULIN		GAMMA GLOBULIN INTRAMUSCULAR		CEPHALIN FLOCCULATION						GLOBULIN REQUIRED IN VITRO
								1ST DAY		2ND DAY		3RD DAY		
				24 HR.	48 HR.	TOTAL	C.C./KG.	24 HR.	48 HR.	24 HR.	48 HR.	24 HR.	48 HR.	
1.	10	35	Scarlet fever	0	0	20 c.c.	0.57			++	+++	0	++	1:250
2.	8	26	Scarlet fever	0	0	20 c.c.	0.75					+	+++	1:250
3.	½	5	Hirschsprung	0	0	2.1 c.c.	0.42	++	++++	0	+			1:200
4.	½	6.8	Encephalitis	0	0	3.0 c.c.	0.44	++	++++					1:300
5.	1	9	Diarrhea	0	0	2.0 c.c.	0.22	0	+			0	+	1:300
6.	2	12.5	Pneumonia	0	0	2.0 c.c.	0.15	0	0					1:800
7.	2	13.5	Impetigo	0	0	3.0 c.c.	0.22	0	0					1:800
8.	½	6	Diarrhea	+	++	2.6 c.c.	0.44	+	++					1:800
9.	7	23	Pharyngitis	0	+	5.0 c.c.	0.22	0	++					1:1000
10.	11	27	Pneumonia	0	0	5.0 c.c.	0.18	+++	++++					1:1000

widely used. The idea was conceived that large dosages of this preparation might influence the outcome of the cephalin-cholesterol flocculation. To see if this were true, ten patients were given gamma globulin intramuscularly, and blood was removed from the patient twenty-four and forty-eight hours later. At the same time, a dilution of the gamma globulin preparation used in each case was tested to find the lowest concentration necessary to produce a positive test in vitro. This was found to vary markedly with the product. The first five patients received Armour's immune globulin and the remaining patients received Cutter's* immune globulin. When 0.2 c.c. of the diluted material was used, it was found that dilutions of Armour's globulin below 1:300 was necessary, while the Cutter's globulin was active in vitro in 1:800 to 1:1000 dilutions. It was soon noted that different preparations of the cephalin-cholesterol water suspension varied in their sensitivity, and a control of distilled water and a known positive serum was necessary to evaluate the experiment. The procedure was performed in the same manner as described above for the premature infants, with the exception that the blood was usually obtained from the antecubital fossa.

As can be seen in Table II, the majority of the patients had a positive flocculation after the administration of the globulin intramuscularly. Three (patients 1, 2, and 5) continued to give these findings for at least seventy-two hours. Three others (patients 6, 7, and 8) showed no changes, although the globulin used was very active in vitro. The last (patient 10) had a 4+ reaction after receiving less of the same preparation. From these findings it appears that to evaluate properly a positive flocculation of a child, information should be obtained as to whether or not the patient may have recently received an injection of immune globulin.

SUMMARY

1. The cephalin-cholesterol flocculation is positive in premature infants during the first week of life, and often throughout the second.

2. The cephalin-cholesterol flocculation appears to be influenced when large amounts of immune globulin are given intramuscularly.

3. The cephalin-cholesterol flocculation is subject to many variable factors capable of producing false positive results.

REFERENCES

1. Hanger, F. M.: Flocculation of Cephalin-Cholesterol Emulsions by Pathological Sera, Tr. Asso. Am. Physicians 53: 148, 1938.
2. Neefe, J. R., and Reinhold, J. G.: Photosensitivity as a Cause of Falsely Positive Cephalin-Cholesterol Flocculation Tests, Science 100: 83, 1944.
3. Rosenberg, D. H.: The Cephalin-Cholesterol Flocculation Test in Cases of Disease of the Liver With Special Reference to the Diagnosis of Mild and Unsuspected Forms, Arch. Surg. 43: 231, 1941.
4. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation 18: 261, 1938.
5. Salmon, G. W., and Richmond, E. E.: Liver Function in the Newborn Infant, J. PEDIAT. 23: 522, 1943.
6. Moore, D. B., Pierson, P. S., Hanger, F. M., and Moore, D. H.: Mechanism of the Positive Cephalin-Cholesterol Flocculation Reaction in Hepatitis, J. Clin. Investigation 24: 292, 1945.

*Immune Serum Globulin (Human) provided by the American Red Cross.

MEASURING THE SPECIFIC GRAVITY OF SMALL AMOUNTS OF URINE

A Rapid and Simple Method

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IT IS not unusual in pediatric practice to see the specific gravity determination omitted from the report of a urinalysis on young infants, due to the insufficient quantity of the specimen. Indeed it may at times be difficult or at least inconvenient to collect urine specimens of sufficient volume from tiny babies to permit a specific gravity determinatoin by the clinical urinometer, notwithstanding the fact that this is an essential part of the laboratory investigation, particularly in disorders of the kidney or water metabolism.

The method described here makes it possible with a few drops of urine to determine the specific gravity in a few minutes.*

THE METHOD

Drops of urine are allowed to fall into a graded series of oily solutions made up by mixing kerosene and bromobenzene in varying proportions, ranging in specific gravity from 1.000 to 1.060. Note is made in each instance whether the urine drop rises or sinks in the given test solution, in a manner similar to that used in determining blood specific gravities with copper sulfate solutions.[1]

A series of sixteen test mixtures are graded from 1.000 to 1.030 at intervals of 0.002, and eight test mixtures ranging from 1.032 to 1.060 at intervals of 0.004. For the urine, a medicine dropper with a fine capillary tip is used, or a 20 c.mm. hemoglobin pipette, if the quantity of urine is too small. The tip of the pipette is brought about 3 cm. below the surface of the test solution, or to a point slightly above the center of the bottle, and a drop is gently forced out. If the drop is of the same specific gravity as the test mixture, it will tend to remain stationary in the solution; if heavier, it will sink to the bottom of the bottle; and if lighter, it will rise to the surface. According to the result in the first test bottle, others are selected until the value of the unknown has been bracketed by adjacent test solutions or one has been found in which it remains stationary. Thus, the specific gravity can be determined within 0.001 if the unknown is at 1.032 or less, and with 0.002 if denser than 1.032. It is advisable to make the initial trial with the 1.020 bottle and then proceed to 1.030 or 1.010 as indicated.

Although designed for use with small amounts of urine, this method may be employed for determining the specific gravity of other fluids as well.

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*The gradient cylinder method of Linderstrøm-Lang[2] may be used for urine. The present method has the following advantages: the plotting of curves is eliminated; the solutions can be carried about and shaken without ill effect; and the method can be used by any student without technical difficulty.

PREPARATION OF STANDARD SOLUTIONS

Two stock solutions are first prepared, one of 952 ml. with a specific gravity of 1.000 and the other of 668 ml. with a specific gravity of 1.060. It is difficult to give precise figures as to the proportions of kerosene and bromobenzene in these stock solutions, due to the inconstancy in specific gravity of different stocks of the former. However, a kerosene-bromobenzene ratio of 70:30 yields a specific gravity of about 1.000, and one of 62:38 will be approximately 1.060. Solutions of these proportions can be adjusted to exact value by any of three methods:

1. By pycnometry.

2. By the addition of drops of aqueous solutions of known specific gravity, noting whether they rise or fall. For the stock solution of specific gravity 1.000, distilled water may be used as a test substance; for that of 1.060, a solution of 9.850 Gm. copper sulfate ($CuSO_45H_20$) in 100 ml. of water at 18° C.[5] will be adequate.*

3. By use of a certified clinical urinometer which has been tested for accuracy on solutions of known specific gravity.

After the two stock solutions are ready, they may be mixed in different proportions as shown in Table I. The stock solutions may be put in two burettes for convenience and delivered directly into the containing bottles, which should be equipped with tightly-fitting screw caps to prevent evaporation and leakage. It will be noted in Table I that to obtain a standard solution of a given specific gravity, the last two figures of the specific gravity give the number of millileters of stock solution B to be diluted to 60 ml. with stock solution A; e.g., to make a solution of specific gravity 1.024, dilute 24 ml. of stock solution B with 36 ml. of stock solution A.

After preparing the twenty-four standard mixtures, it is desirable to check at least several of them by one of the three methods mentioned above.

Since it is recommended that initial trials with unknowns be made with the 1.020, 1.010, and 1.030 bottles, these standards will receive considerably more use than the rest and therefore it is advisable to make them up in extra supply.

USEFUL LIFE OF THE STANDARD SOLUTIONS

Since both the organic and inorganic constituents of urine are practically insoluble in the test mixtures, the specific gravities of the latter have been found so far to remain nearly constant at a given temperature, even after the addition of 80 drops of urine to 60 ml. of test mixture, and over a period of several weeks. However, for mechanical reasons it will probably be found desirable to clear the bottles after the accumulation of this amount of urine.

After the bottles have been shaken, all urine drops will be either at the bottom or the top of the bottle, because by intermingling they will have arrived at a more or less homogenous specific gravity and will separate out from the organic solutions. Urine which has floated to the top may be pipetted off. That

*If in the same laboratory the copper sulfate method for blood and serum specific gravities is in use, it will be found convenient to check both these stock solutions and the subsequently-prepared standard solutions by use of appropriate copper sulfate standards.

which has sunk to the bottom may most advantageously be removed with a separatory funnel; specifically, an ordinary burette may be used for this function. Filtering is another convenient and satisfactory way of clearing the standard solutions.

Notwithstanding the above, after the lapse of eight to ten weeks of use it may be a desirable precaution to test the mixtures by one of the methods mentioned elsewhere and to adjust them if necessary by the addition of drops of kerosene or bromobenzene.

TABLE I. MILLILETERS OF STOCK SOLUTIONS OF GRAVITIES 1.000 AND 1.060 TO BE MIXED TO PREPARE 60 ML. OF STANDARD TEST SOLUTIONS OF GRAVITY G*

NO.	G	A	B	NO.	G	A	B
1	1.000	60	–	13	1.024	36	24
2	1.002	58	2	14	1.026	34	26
3	1.004	56	4	15	1.028	32	28
4	1.006	54	6	16	1.030	30	30
5	1.008	52	8	17	1.032	28	32
6	1.010	50	10	18	1.036	24	36
7	1.012	48	12	19	1.040	20	40
8	1.014	46	14	20	1.044	16	44
9	1.016	44	16	21	1.048	12	48
10	1.018	42	18	22	1.052	8	52
11	1.020	40	20	23	1.056	4	56
12	1.022	38	22	24	1.060	–	60

G, Gravity of standard test solutions.
A, Stock solution of specific gravity 1.000.
B, Stock solution of specific gravity 1.060.
*A total of 952 ml. of A and 668 ml. of B needed for the entire set, numbers 6, 11, and 16 being prepared in duplicate as recommended.

THE EFFECT OF TEMPERATURE

The difference in coefficient of expansion between urine and those of the standard solutions is such as to introduce an error of 0.002 to 0.003 in the temperature range from 14° C. to 30° C. if the standard solutions are prepared at 22° C. However, it has been repeatedly shown that with ordinary urinometers much wider discrepancies are found with changes in temperature,[3] and different urinometers sometimes give widely different specific gravity readings.[4] It is felt, therefore, that the present method is of satisfactory accuracy for clinical use.

PRECAUTIONS

1. At least once a day the standard bottles should be shaken or inverted once or twice. This should be done before using if they have not been agitated for more than twenty-four hours. However, they must be allowed to stand for three to four minutes for gross currents to have subsided before drops of urine are introduced.

2. Occasionally, a drop of urine will not readily detach itself from the pipette. It may then be of help to move the pipette rapidly back and forth in a horizontal direction.

3. It is preferable to use small drops of urine for the reason that they permit more tests before the standard solutions need be cleared.

SUMMARY

A simple method has been described, for determining the specific gravity of urine with a few drops of specimen, and of satisfactory accuracy for clinical use.

REFERENCES

1. Philips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Hamilton, P. B., and Archibald, R. M.: The Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, Bull. U. S. Army Med. Dept. 1: 66, 1943.
2. Jacobsen, C. F., and Linderstrøm-Lang, K.: Method for Rapid Determination of Specific Gravity, Acta Physiologica Scandinavica 1: 149, 1940.
3. Windsor-McLean, L. A.: Temperature as a Factor to Be Considered in Clinical Urinometry, Med. J. Australia 2: 467, 1938.
4. Aaron, H.: The Accuracy of Clinical Urinometers, Am. J. Clin. Path. (Technical Section) 9: 70, 1945.
5. Computed from value quoted from Schiff and Gerlach in Handbook of Chemistry and Physics, ed. 24, Cleveland, Ohio, 1940, Chemical Rubber Publishing Co., p. 1517.

ADDENDUM

After submission of this paper, the writer's attention was called to a similar method published recently by Monroe and Hopper, using xylene instead of kerosene (J. Lab. and Clin. Med. 31: 8, p. 934). It is felt that the method herein described has certain advantages over theirs. In the first place, the present method allows a much larger margin of error in the preparation of standards, viz: An increment in specific gravity of 0.001 is produced in their method by a difference of only 0.16 ml. of stock solution in a 100 ml. standard, whereas in using stock solutions described in this paper such an increment requires one millimeter in 60 ml. of standard. Thus their standards differ consecutively in specific gravity by 0.005, whereas in the present method by only 0.002, permitting a greater accuracy in results. Secondly, kerosene is considerably cheaper and more readily available than xylene.

RELATIONSHIP OF WEIGHT AND LENGTH OF INFANTS AT BIRTH TO THE AGE AT WHICH THEY BEGIN TO WALK ALONE

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THE contention that heavier children are likely to learn to walk later than lighter ones is more than a mere popular belief, although little scientific evidence which supports that conclusion has been recorded. Shirley,[1] who observed twenty-five babies during their first two years of life, stated that the muscular and small-boned babies walk alone earlier than the short, rotund babies or the exceedingly heavy ones. She suggested that retardation in motor development of two or three of the children she observed may have been due to their large size. Peatman and Higgons[2] quoted Louttet, who stated that the age of walking was affected to some extent by the weight of the child. Strang[3] wrote that the slender, linear child walked at an earlier age than the broad, heavy child. Strang stated that girls tend to walk at an earlier age than boys. Terman[4] found that among 565 gifted children, the girls were more precocious than the boys in walking. Peatman and his associate found that among 349 normal infants, correlations were of zero order between the age at which the infants started to walk and the relative weight and indices of bodily build at the time. It seemed appropriate to find whether an objective and quantitative examination of available data would reveal any relationship between the age at which the children began to walk and their length and weight at birth.

The data utilized were obtained on 194 normal babies who were observed periodically from birth to the latter part of the second year. The weight and length at birth were noted to the nearest gram and centimeter, respectively, and converted to pounds and inches. The age at which the child walked alone was defined as the age when he began to take several steps alone. In most instances this date was obtained from the mother when she brought her infant for his monthly visits, and while this method may be subject to considerable inaccuracy if the history is obtained weeks or months later, it should be fairly definite when taken at such frequent checkup visits during the period at which the accomplishment occurs.

In the group of infants studied, ninety-nine were boys and ninety-five were girls. The mean age at which the male infant began to walk was 11.97 ± 0.16 months, which does not differ statistically from the mean age of 11.84 ± 0.21 months computed for the girls.

The weight of the infants at birth and the age at which they first walked alone showed a slightly inverse relationship. The correlation coefficient for these two variables was -0.09, which is not statistically significant. The random probability of getting a negative correlation as large as 0.09 in samples of this size is 0.3; only probability values equal to or less than 0.05 generally are considered to be statistically significant.

Contrary to expectation the babies who were longer at birth were found to have walked alone at an earlier average age than the shorter ones. The upper 25 per cent in order of length, that is, the forty-eight longest ones (mean length: 20.7 ± 0.07 inches), started to walk when they were 11.4 ± 0.24 months old, while the forty-eight shortest babies (mean length: 18.7 ± 0.05 inches) started to walk when they were 12.5 ± 0.25 months old. The difference in the age of walking alone of the longest and the shortest 25 per cent of the series is a little more than one month. The correlation coefficient for these two variables was –0.27. Since the probability of getting a negative correlation as large as 0.27 in this sample is 0.04, this relationship may be considered statistically significant. The linear equation for prediction of age at which a child will begin to walk from length alone was

$$\text{Age} = 21.97 - 0.51\ \text{L}$$

in which age is given in months and L represents length at birth in inches. It is to be noted that the original data in respect to age at which the child first walked alone were obtained during interviews with the mother and were not observed directly. Any inaccuracy in this will be reflected in a lower apparent correlation as obtained from the calculations. Therefore it may be said that with more precise data in these records it is likely that a somewhat greater, but still small, correlation with length would have been found. Consequently, it is indicated that length is a factor, but by itself is only a relatively unimportant one, in determining the age at which an infant will begin to walk.

Next, the age at which the child started walking was investigated in relation to the weight and length at birth taken together. The partial correlation of age at which the child began to walk alone with length, for constant weight, was –0.29. The partial correlation of age at which the child began to walk alone with weight, for constant length, was +0.13. The multiple correlation coefficient for both variables together was 0.30 (P = 0.03, statistically significant). The linear equation for predicting age at which a child will walk alone from length and weight together was found to be

$$\text{Age} = 24.33 - 0.73\ \text{L} + 0.26\ \text{W}$$

in which W represents weight of the child at birth in pounds. In studying the partial correlations and the equation in terms of length and weight, an attempt was made to determine the relationship of age at which the child begins to walk alone, on the one hand, with length of babies all of the same weight at birth and on the other hand, with weight for babies all of the same length at birth. Equation 2 indicates that for infants of any given weight, an increase of an inch in length decreases the average age at which the baby starts walking by about twenty-two days. For infants of any given length, on the other hand, an increase of a pound in weight at birth increases the age at which the child begins to walk, on the average, by about eight days. Thus, it is apparent that infants who are longer for their weight walk at an earlier age than those who

are relatively short for their weight, corroborating the opinion of Strang previously mentioned that children of the linear type of build walk alone at an earlier age.

The relationship of the age at which a child begins to walk to weight and length was investigated also by relating age to the index W/L^3. The correlation found with this index was +0.20, indicating again that the babies who are heavier for their length begin to walk later, but the correlation was brought out more definitely by use of the linear equation ($R = 0.30$), than by the index W/L^3.

SUMMARY AND COMMENT

The relationship of the age at which 194 babies began to walk alone to their length and weight at birth was investigated. Ninety-nine of the babies were boys and ninety-five were girls. The average age at which girls began to walk alone was only slightly earlier (11.84 ± 0.21 months) than that at which boys began to walk alone (11.97 ± 0.16 months). However, when the size of the group investigated is considered, this difference is not statistically significant. No significant correlation was found between age at which the babies started walking and weight at birth considered by itself.

The length at birth was found to be correlated negatively with age at which the babies began to walk ($r_{AL} = -0.27$). An increase of an inch in length was associated with a decrease of an average of about fifteen days in the age at which the child began to walk.

The greatest correlation found was when length and weight were considered together ($R = 0.30$). For babies all of the same weight, an increase of an inch in length was associated with a decrease of an average of twenty-two days in the age at which the child began to walk and for infants of the same length, an increase of a pound in weight at birth was associated with an increase of an average of eight days in age of walking alone. The infants who were relatively long for their weight, therefore, began to walk at an earlier age than the others.

In view of the rather small number of cases included in the study, the results cannot be considered definitive until corroborated with observations in a larger number of cases.

REFERENCES

1. Shirley, Mary M.: The First Two Years; a Study of Twenty-five Babies, Minneapolis, 1931, The University of Minnesota Press, vol. 1, pp. 114-126.
2. Peatman, J. G., and Higgons, R. A.: Am. J. Orthopsychiat. 12: 234, 1942.
3. Strang, Ruth M.: An Introduction to Child Study, New York, 1938, The Macmillan Company, pp. 58 and 171.
4. Terman, L. M.: Genetic Studies of Genius, 1925, Stanford University Press, vol. 1, p. 187.

Case Reports

ATRESIA OF THE ILEUM

First Successful Case Cured by Enterostomy Alone

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ATRESIA of the intestinal tract is, fortunately, a rare condition, appearing about once in 20,000 babies, according to Farr and Brunkow.[1] The condition was first described by Calder[2] of Edinburgh in 1733, in the *Medical News* under the title, "Two Examples of Children Born With Preternatural Conformation of the Guts."

Numerous theories have been advanced for the etiology of this condition. In 1889, Sutton[3] wrote, "Congenital obstructions and narrowing of the alimentary canal are always found in the situation of embryologic events. Imperforate ileum occurs in the region where the primitive alimentary canal is in communication with the yolk-sac by means of the vitelline duct." The most plausible explanation seems to be that atresia results from an arrest of development in the embryo when, for some unknown reason, the intestinal tube fails to clear itself of the epithelial concrescences. This process is well illustrated by the accompanying pictures (Figs. 1 and 2) from *Abdominal Surgery of Infancy and Childhood* by Drs. Ladd and Gross.[4]

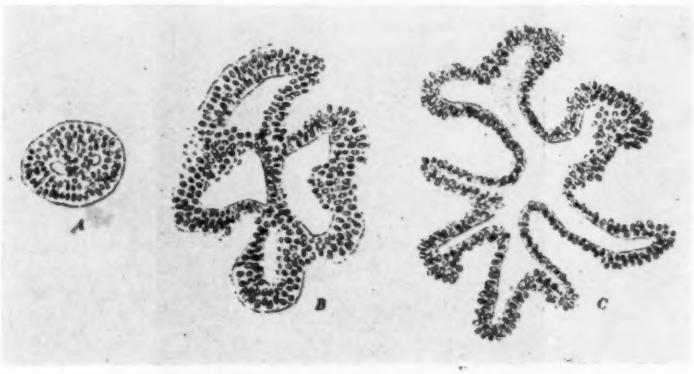

Fig. 1.—*A*, Concrescence of intestinal epithelium after five weeks of fetal life; *B*, showing formation of cystic spaces; *C*, intestinal lumen cleared by twelfth week. (From Ladd and Gross after Keibal and Mall.)

The site of the atresia may be anywhere in the intestinal tract, although the colon is rarely involved. In 1922, Davis and Poynter[5] collected 392 cases, in which 101 were located in the ileum and colon. Less than one-third of these reported cases were subjected to laparotomy. Ladd and Gross,[4] in 1941, stated that in fifty-two cases of atresia, thirty-four were located in the ileum.

In 1889, Sutton[3] correctly diagnosed what he called "imperforate ileum" and performed an enterostomy. The atresia was eighteen inches from the ileocecal valve. "The child rallied and took food, but about six hours later it

From the surgical department of Queen's Hospital.

suddenly expired." Sutton[3] concluded that this was the first case of atresia diagnosed during life and operated upon. He was evidently unaware that Von Tischendorf[6] had reported a patient with enterostomy on the seventh day who survived for fifteen days.

No baby born with intestinal atresia lived until the year 1911, when Fockens[7] of Rotterdam reported a case of atresia of the ileum successfully cured by lateral anastomosis. Ten years later Demmer[8] of Vienna reported a cure by the same method. In 1933, Carter[9] had a successful outcome following lateral anastomosis between ileum and descending colon plus ileostomy. Ladd and Gross[4] report three successful cases of atresia of the ileum cured by primary anastomosis.

In 1931, Webb and Wangensteen[10] published a thorough but lugubrious article, reporting fifteen fatal cases of atresia of the intestinal tract, of which six patients were submitted to operation and the diagnoses of the remaining nine were confirmed at autopsy. The authors concluded that "anastomotic procedure is the only operation that holds any promise of success. The establishment of a complete external intestinal fistula in the infant is doomed to failure from the start. No instance of recovery following enterostomy has occurred."

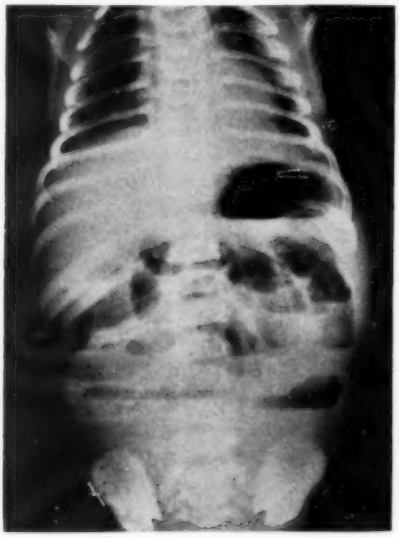

Fig. 2.—Typical x-ray findings.

In 1939, Miller[11] wrote: "There has never been a successful result recorded where ileostomy alone has been used. A short circuiting lateral anastomosis offers the only hope of success." Ladd and Gross[4] (1941), as the result of their extensive surgical experience, conclude that "ileostomy is a poor surgical procedure. To our knowledge there has been no case in the literature which has been successful with enterostomy alone."

It is perhaps fortunate that the author had not seen the articles quoted before April 28, 1946, when he was called to operate on a 3-day-old Chinese baby with atresia of the ileum. As the baby made a complete recovery with ileostomy alone, the case is reported in considerable detail.

A Chinese female, a second child, was born by a normal delivery with a birth weight of 7 lbs., 14 oz. Vomiting started after the first feeding. The baby had several bowel movements. Nothing unusual was noted as to the meconium. Farber's[12] test (absence of cornified epithelium in the meconium) was not done, as we were not acquainted with the test. Abdominal distention appeared soon and developed to a marked degree. Bile-tinged vomiting continued. No visible peristalsis was observed. The veins of the abdominal wall were distended. There were a few peristaltic sounds heard with the stethoscope. Dehydration was marked. There was slight fever. X-ray findings were typical of small intestinal obstruction with fluid level.

The preoperative diagnosis was obstruction of small intestine.

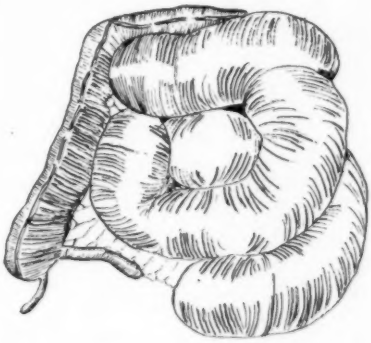

Fig. 3.

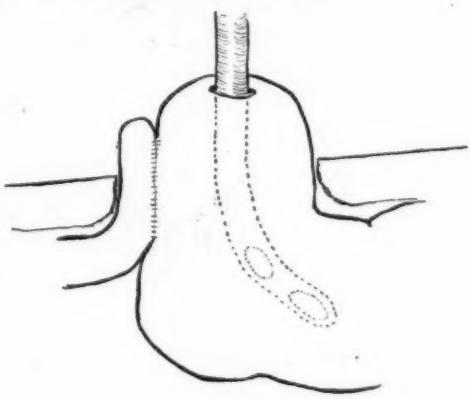

Fig. 4.

Fig. 3.—Diagram of operative findings. Proximal loop greatly thinned out and distended. Distal segment and colon contracted. Gap of 2 inches between rounded ends.

Fig. 4.—Operative procedure on third day. First stage.

First Operation.—April 28, 1946. After lavage of the stomach and administration of parenteral fluids, under drop ether anesthesia a laparotomy was performed through a right rectus incision. Considerable clear, peritoneal fluid was evacuated and the atresia was found without difficulty in the lower ileum about 3 inches from the ileocecal valve. There was a gap of 2 inches between the two rounded ends of the segments. The proximal bowel was extremely distended about 4 cm. in diameter and the wall was thinned out. The distal segment was the size of a cigarette. There was a V-shaped gap in the mesentery and there was no fibrous strand connecting the two rounded intestinal ends. The colon was contracted to the size of an adult index finger. The two segments were sutured together with fine cotton and exteriorized. The gap in the mesentery was closed. A No. 12 catheter was inserted into the proximal bowel and the abdominal wall was partly closed without suturing the intestine to the peritoneum. Thin, brownish material drained at once per catheter, the distention subsided, and after recovery from the anesthetic, the baby ceased vomiting. Inhalations of oxygen were given with apparent benefit and a Wangensteen tube was inserted.

Second Operation.—May 2 (no anesthetic). The catheter was removed. The ends of the protruding intestine were incised. The distal segment had dilated to an amazing degree. The septum was incised for about an inch and the intestinal walls were sutured with fine chromic gut. A small Kocher clamp was applied to the balance of the spur. This procedure was undertaken in order

to provide the possibility of some intestinal contents passing at once from the proximal to the distal loop. In forty-eight hours the baby had a movement by rectum. The clamp was tightened every day and cut through on the fourth day. A finger, inserted in the stoma, showed a large communication between the two loops, the calibre of which was greater than the intestinal calibre. As recommended by Ladd and Gross,[4] enemas of saline solution were given twice

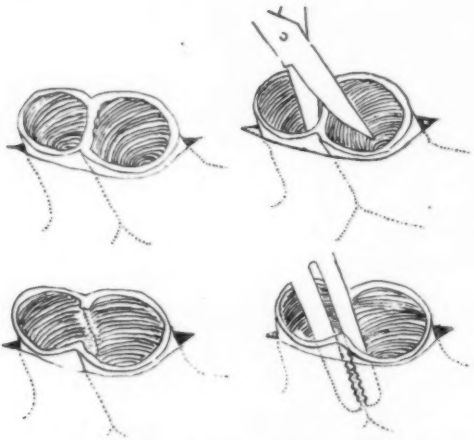

Fig. 5.—Operative procedure four days later. Incision of septum and suture of intestinal wall and small Kocher clamp applied to lower part of spur.

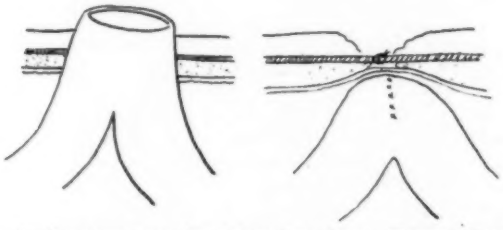

Fig. 6.—Ileostomy open for eighty-three days. Closure of same.

a day in order to distend the colon. The feces were discharged about half by the stoma and half by rectum. There was a surprising amount of fluid loss from the enterostomy. The surrounding skin became excoriated. Starch powder applied liberally was found effective in counteracting the irritation. As the protruding intestinal ends began to slough, there were several small hemorrhages which were readily controlled by sutures. The baby held her own and began to gain weight. The plan then was to close the enterostomy when it had contracted and when the major part of the feces was being passed by rectum. This procedure was based on the practice adopted in surgery of adults, usually a six-week to two-month period being allowed for the intestinal stoma to contract. In a crying baby conditions are different. The stoma refused to contract, natural bowel movements became less and less and finally ceased and when the baby cried, the lowest part of the stoma began to prolapse.

Third Operation.—July 9 (drop ether anesthesia). This consisted of an attempt at closure of the enterostomy by the method usually used in surgery

of adults. This operation was an ignominious failure. The wound held for eight days and then broke down and conditions were as before.

Fourth Operation.—July 24 (drop ether anesthesia). The bowel was freed at the mucocutaneous junction, the edges pared and sutured with Connell cotton stitches. The skin margins were dissected back and strands of fascia and atrophic muscle were carefully sutured over the intestinal wound with fine steel wire. A light petrolatum gauze pack was placed in the wound and the skin edges were left open. A rubber pad was held on the wound by a spica ace bandage. There was a considerable discharge from the wound of a thin, watery fluid for a few days but no fecal matter. The wound healed solidly and the baby was discharged August 21 in good condition, weighing 10 lbs., 1 oz.

Fig. 7.—Baby on discharge from hospital, 118 days old (weight, 10 lb., 9 oz., birth weight, 7 lb., 14 oz.), showing healed wound.

Supplementary Therapy.—During her stay in the hospital, the baby received thirteen whole blood transfusions, given into the scalp veins by the pediatricians. The amazing loss of fluids from the stoma was vigorously combatted by hypodermoclyses, forty-seven in all. Water and electrolytes were supplied by Lactate-Ringer solution and glucose; plasma and vitamins were given according to indications. Penicillin was administered in eighty-three doses of 10,000 units each. Some sulfadiazine was given and a course of sulfasuxidine for five days before the last operation. The baby was fed breast milk at first and then was put on a formula with iron and vitamins added to the mixture.

COMMENTS

1. A report is made of a case of atresia of the lower ileum cured by enterostomy alone. According to the literature, this is the first cure recorded by this method.

2. It should be distinctly understood that a successful outcome by ileostomy alone can only be expected when the atresia is located low in the ileum. An atresia higher up in the ileum or in the jejunum must be treated by a primary anastomosis.

3. An ileo-ileostomy in a newly born baby is a time-consuming and delicate operation with a high mortality. In case the atresia is low down in the ileum, the question arises whether an ileostomy with early division of the spur is not a wiser procedure.

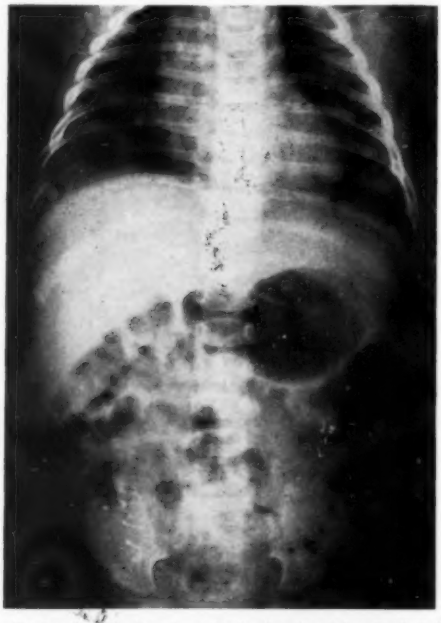

Fig. 8.—X-ray taken September 6, showing steel wire in abdominal wall and normal colon.

4. This report shows that a baby can survive with enterostomy alone provided the atresia is in the lower ileum. The dehydration and malnutrition must be combatted vigorously. Nowhere in the field of medicine is teamwork between physician and surgeon more important than in a condition of this kind, where nutrition means everything.

5. In retrospect, at least two mistakes were made. Following the practice in surgery of adults, we expected the stoma to contract and waited in vain for this to occur. The closure of the stoma should be done when the mucocutaneous junction is well formed, perhaps between the third and fifth week. The second mistake was in the method of suture. In the operation that failed, the bowel wall was freed and sutured and through-and-through silk stitches brought the abdominal wall together. By this method the sutured intestinal line does not receive sufficient support to counteract the explosive effect of the baby's cries. Also, the skin should not be sutured. Steel wire made an admirable suture material.

My thanks are due to the pediatricians, Drs. D. C. Marshall, F. D. Nance, and C. M. Florine, to the devoted and efficient Japanese nurses, to Drs. R. G. Hunter and K. B. Conger for their able assistance, and to Dr. Conger for the drawings.

REFERENCES

1. Farr, R. E., and Brunkow, C. W.: Congenital Abnormalities of the Intestines, Arch. Surg. **11**: 417, 1925.
2. Calder, J.: Two Examples of Children Born With Preternatural Conformation of the Guts, Med. Essays, Edinburgh **1**: 203, 1733.
3. Sutton, J. Bland.: Imperforate Ileum, Am. J. Med. Sc. **98**: 457, 1889.
4. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1941, W. B. Saunders Co.
5. Davis, D. L., and Poynter, C. W. M.: Congenital Occlusion of the Intestines, Surg., Gynec. & Obst. **34**: 35, 1922.
6. Tischendorf, V.: Enterostomie bei angeborener Atresie des Ileum. Beilage z. Zentralbl., f. Chir. **14**: 69, 1887.
7. Fockens, P.: Ein operativ geheilter Fall von Kongenitaler Dünndarm-atresie, Zentralbl. f. Chir. **38**: 532, 1911.
8. Demmer, F.: Atresia Ilei, Arch. f. klin. Chir. **147**: 471, 1927.
9. Carter, R. F.: Congenital Occlusion of the Duodenum and Small Intestine, J. PEDIAT. **2**: 27, 1933.
10. Webb, C. H., and Wangensteen, O. H.: Congenital Intestinal Atresia, Am. J. Dis. Child. **41**: 262, 1931.
11. Miller, E. M.: Bowel Obstruction in the Newborn, Ann. Surg. **110**: 587, 1939.
12. Farber, S.: Congenital Atresia of the Alimentary Tract: Diagnosis by Microscopic Examination of Meconium, J. A. M. A. **100**: 1753, 1933.

SEXUAL PRECOCITY AND ACCELERATED GROWTH IN A CHILD WITH A FOLLICULAR CYST OF THE OVARY

GEORGE C. KIMMEL, M.D.
RED WING, MINN.

PREMATURE development of the genital organs associated with an increase of body size may be due to various causes. These can be conveniently classified into three groups:

1. Those due to endocrine disorders such as hyperplasia or neoplasms of testicular, ovarian, or cortico-adrenal cells.

2. Those due to changes in the central nervous system, consisting chiefly of intracranial tumors. These are usually located near the floor of the third ventricle and presumably have an irritating or stimulating effect on the anterior pituitary gland, which in turn stimulates the gonads.

3. A poorly defined group in which no lesion can be found, a so-called constitutional group.

There is also a syndrome, first described by Albright[1] in 1937, the etiology of which is as yet unknown, but which has been suspected as being due to some disturbance in the central nervous system. This syndrome consists of disseminated fibrosis of bone, extensive patchy areas of cutaneous pigmentation, precocious growth, and, among females, precocious sexual development.

In young females with precocious sexual development there is usually hypertrophy of the breasts, uterus, and labia, and often the appearance of pubic and axillary hair. Frequently there is uterine bleeding, or precocious menstrual periods, and in some cases a marked increase in body size. In some of these patients, even very young girls, pregnancy is possible. However, according to Novak,[2] this possibility exists only among those of the constitutional type.

The urinary excretion of estrogens has been found to be markedly elevated in most patients with granulosa cell tumor of the ovary as well as in some of those with hyperplasia or tumor of the cortico-adrenal cells. In those with cortico-adrenal tumors, however, an increase in the urinary excretion of alpha and beta 17-ketosteroids is also found, while no such increase is present in those with granulosa cell tumor of the ovary.

The number of reported cases of ovarian tumors associated with precocious sexual development among children is small. Lull,[3] in a review of the literature published in 1941, was able to collect only sixteen reported cases in which granulosa cell tumor of the ovary was responsible for premature sexual development. He added one case, that of a 9-month-old infant, the youngest so far reported. He also reported, in the same article, a case of premature sexual development in a 22-month-old girl. A granulosa cell tumor was suspected, but at operation she was found to have a follicular cyst of the ovary. This child's symptoms regressed and the sexual development reverted to the infantile type following surgical removal of the cyst. Quantitative examination of this child's urine preoperatively showed the absence of any measureable amount of estrogen.

Fischer,[4] in 1940, reported the case of a 4-year-old girl with the characteristic changes of sexual precocity, including periodic vaginal bleeding for eight months, enlarged breasts, nipples, labia, and increased height. Quantitative urinary pregnanediol determinations preoperatively showed results comparable to those found in the early months of pregnancy (31 mg. of pregnanediol glucuronate). At operation the left ovary was removed and was found to contain many small cysts, the largest being 1.2 cm. in diameter. No evidence of granulosa cell tumor was found. Up to the time of publication of his case report,

five months after the operation, there had been no recurrence of the vaginal bleeding. However, no very marked decrease in size of the breasts, nipples, or labia had occurred up to that time. No mention was made regarding postoperative urinary hormonal studies. Fischer concluded that he preferred to assign his patient to the constitutional group rather than to attribute the precocious development to the cysts found in the ovary.

Fig. 1.—Appearance of the patient at time of first examination.

Additional observations over a longer period of time in Fischer's case would be of considerable interest. If this patient were of the constitutional type, the symptoms and changes in body development would be expected to continue despite removal of the cystic ovary. As stated previously, the vaginal bleeding had not recurred up to five months postoperatively. One wonders if this did recur later on and whether or not there was a subsequent return of the breasts and labia to normal size.

Except for the two previously mentioned cases reported by Lull and Fischer, no references in the literature were found similar to the case here reported, in which the precocious changes were associated with, and apparently caused by, a follicular cyst of the ovary.

CASE REPORT

This case is that of a female, white child, 25 months of age. The family history is noncontributory and the past history is essentially negative.

The presenting complaint was vaginal bleeding, which first occurred on May 23, 1942. There was approximately one tablespoonful of blood present in the child's underclothing. A very slight mucoid vaginal discharge had been present for three days prior to the onset of bleeding.

Examination of the patient on May 23 showed a moderate but very definite hypertrophy of the breasts and nipples, with quite prominent pigmentation about the nipples. The labia minora were moderately enlarged. Abdominal examination revealed no apparent enlargement of the liver or spleen, and no masses could be felt in the kidney or adrenal regions. Combined rectoabdominal examination revealed a moderately enlarged uterus slightly to the left of the midline, but no definite mass was palpated in either adnexal region.

The child was very tall for her age, her height being 39½ inches, her weight 31½ pounds. According to the table of height curves prepared by Burgess,[5] the average height for girls of this age is 34½ inches while 99 per cent are less than 38 inches tall. This patient was 5 inches taller than the average and 1½ inches taller than the 99 per cent curve.

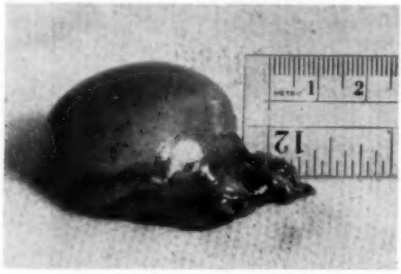

Fig. 2.—Surgical specimen showing appearance of right ovary and tube.

The vaginal bleeding lasted for two days. It did not recur.

It was quite evident that we were dealing with a case of sexual precocity with accelerated growth, but its cause was not yet clear. Four possibilities were considered: (1) constitutional type of sex precocity; (2) granulosa cell tumor of the ovary; (3) neoplasm in the region of the third ventricle of the brain; and (4) either hyperplasia or tumor of the cortico-adrenal cells.

Examination of the eyegrounds showed no abnormalities, the tendon reflexes were equal and normal, x-ray films of the skull were normal, and an intravenous urogram showed no abnormalities. Blood pressure was within normal limits. The urine examination was normal as was the hemoglobin, leucocyte count, and differential leucocyte count. A chest x-ray was negative. X-rays of the wrists showed normal bone development. Her mental development was normal. There were no pigmented areas of the skin, and x-rays of the long bones were normal. The tuberculin test was negative.

Quantitative determinations of urinary estrogen and ketosteroids were done by Dr. Leo Samuels. He reported finding a greatly increased amount of estrogen (30 I.U.). Doctor Samuels stated that this was as much estrogen as would be contained in the urine of a mature woman during the first week after menstruation. There was no abnormal increase in the urinary ketosteroids.

On the basis of these findings, a tentative diagnosis of granulosa cell tumor of the ovary was made, and operation was advised.

Dr. Irvine McQuarrie saw the patient in consultation at this time. His findings and conclusions coincided with those outlined.

On June 4, 1942, operation was performed by Dr. R. F. Hedin under open drop ether anesthesia. Upon opening the peritoneal cavity, the uterus was

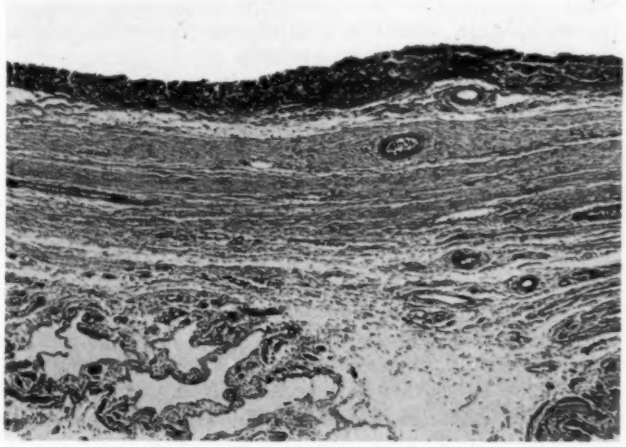

Fig. 3.—Photomicrograph (×60) of section through cyst wall.

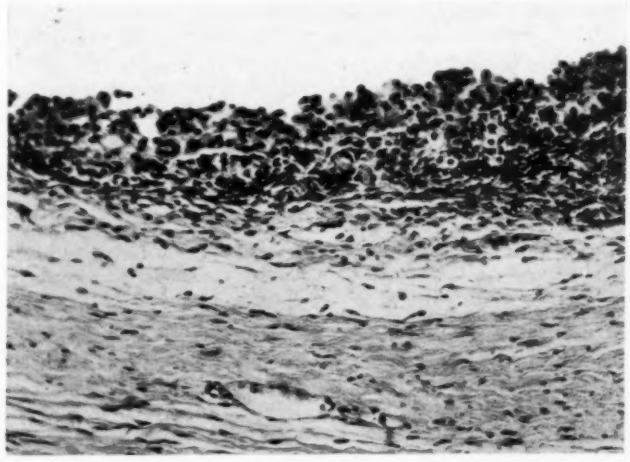

Fig. 4.—Photomicrograph (×200). The dark-staining layer of cells is granulosa cells lining the cyst.

found to be moderately enlarged, and the left ovary appeared to be normal. The right ovary consisted chiefly of a cyst 4 by 3 cm. in diameter, which had destroyed most of the ovarian tissue. A right salpingo-oophorectomy was performed.

The entire specimen was sent intact to Dr. A. C. Broders, who was unable to find any evidence of a granulosa cell tumor. Drs. Robert Meyer and Malcolm Dockerty, who also saw the sections from this cyst, classified it as a follicular cyst of the ovary. It was Dr. Meyer's impression that sufficient estrogen to cause the changes noted in this patient might have been produced by the granulosa cells which lined the cyst.

One month following the operation, and again eighteen months later (January, 1944), quantitative determinations of urinary estrogen and ketosteroids were made by Dr. Samuels. All of these determinations showed normal values for both estrogens and ketosteroids.

Three months after the operation the breasts had decreased considerably in size. It has now been four years and four months since the cyst was removed. The patient has been seen several times during this period. There has been no recurrence of vaginal bleeding, and the labia, uterus, and breasts have regressed to normal size. There have been no additional complaints of any kind. Her height, however, remains proportionately as great as before. When last examined, on Sept. 6, 1946, her height was 51½ inches, her weight 53 pounds. This is about 6 inches above average height and 1½ inches taller than 99 per cent of girls her age.

SUMMARY

1. Sexual precocity with accelerated somatic growth due to ovarian tumors or cysts is relatively rare. Approximately twenty cases in young girls caused by granulosa cell tumors of the ovary have been reported.

2. A case of this character in a 25-month-old girl is reported. She had all of the changes one would expect to find in a case of granulosa cell tumor of the ovary, including a greatly increased urinary estrogen level. At operation, the right ovary was found to consist chiefly of a cyst 4 by 3 cm. in diameter. Following its surgical removal, careful search showed no evidence of a granulosa cell tumor. The cyst was classified as a follicular cyst of the ovary.

The patient has been observed for over four years since the operation. There has been no recurrence of vaginal bleeding. The breasts, nipples, and labia have regressed to their normal size. The estrogen content of the urine has decreased to a normal level and remained normal.

3. A search of the literature revealed only two previously reported cases similar in some respects to the case reported here.

Grateful acknowledgment is made to Dr. Irvine McQuarrie for his kindness in examining the patient and for his helpful suggestions, to Dr. John McKelvy for his interest in the case, to Dr. Leo Samuels who performed the urine assays, and to the pathologists who examined the specimen, Dr. A. C. Broders, Dr. Robert Meyer, and Dr. Malcolm Dockerty, who also prepared the photomicrographs.

REFERENCES

1. Albright, F., Butler, A. M., Hampton, A., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation, and Endocrine Dysfunction, With Precocious Puberty in Females: Report of 5 Cases, New England J. Med. 216: 727, 1937.
2. Novak, E.: The Constitutional Type of Female Precocious Puberty With a Report of 9 Cases, Am. J. Obst. & Gynec. 47: 20, 1944.
3. Lull, C. B.: Pubertas Praecox Due to Ovarian Tumors, Am. J. Obst. & Gynec. 41: 445, 1941.
4. Fischer, H. S.: Precocious Menstruation, Am. J. Obst. & Gynec. 39: 525, 1940.
5. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, 1940, D. Appleton-Century Co., p. 25.

CONGENITAL THROMBOCYTOPENIC PURPURA

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ST. LOUIS, MO.

CONGENITAL thrombocytopenic purpura is a rare condition, but it does occur often enough so that it must be considered as a possible cause of bleeding tendencies in a newborn infant. There have been twenty cases previously reported, and it may be well to review briefly these previous reports before presenting our own cases. Sanford,[1] in 1936, reviewed the literature of twelve cases and presented the case of a female infant whose mother had also had purpura. Davidson,[2] in 1937, reported thrombocytopenic purpura in an infant whose mother had had a splenectomy for this condition. Whitney,[3] in 1942, and Urbanski,[4] in 1942, each presented reports of two consecutive children of mothers with purpura. Morrison,[5] in 1945, presented a single case, and Schefrin,[6] in 1945, reported thrombocytopenic purpura in an infant whose mother had never had any bleeding tendencies.

We have recently seen thrombocytopenic purpura occur in the neonatal period in three successive offspring of a mother with idiopathic thrombocytopenic purpura treated by splenectomy three years before the first pregnancy.

CASE REPORTS

The mother of these children was first admitted to City Hospital on June 3, 1938, at the age of 17, with menorrhagia, bleeding gums, and petechiae. The red count at this time was 1,110,000; platelets, 1,105; bleeding time, 45 minutes; and clotting time normal, with no clot retraction. Idiopathic thrombocytopenic purpura was diagnosed, and a splenectomy was performed on June 30, 1938, with an uneventful convalescence. Following splenectomy the mother was not seen again until Jan. 17, 1941, when she was seven months pregnant. She had been asymptomatic until two months previously, but for the past two months had been having frequent nosebleeds. Examination at this time showed the platelet count to be 25,000, the bleeding time 30 minutes. She was followed in prenatal clinic for the next two months with weekly transfusions up to the time of delivery. During this time there was no appreciable change in the number of platelets but there was cessation of bleeding.

On March 1, 1941, a full-term female infant, D. H., was born (Chart 1). This baby appeared normal at birth, but six hours after birth petechiae appeared over the body; the platelet count was 8,500; liver and spleen were not palpable. On the fourth day of life, blood appeared in the stools and continued for the next week. On the baby's fifth day, the platelet count had dropped to zero, and it then began to rise spontaneously. Bleeding time was 30 minutes. There was no abnormal bleeding after the tenth day, although the baby received no transfusions until she was 3 weeks old; by this time the platelets had risen spontaneously to 20,000. During the next month she received five transfusions, and the platelets continued to increase, showing a precipitous rise at the age of 5 weeks. She was discharged on May 15, 1941, at the age of 2 months, with 542,000 platelets. For the next eighteen months she was followed in clinic, and during this time the blood picture remained normal.

The mother was next seen again in prenatal clinic on Jan. 30, 1945, six months pregnant; blood examination showed only three platelets per cubic

From the Pediatric Service, St. Louis City Hospital.

millimeter, although there had been no spontaneous bleeding or petechiae. She was again followed in clinic with weekly transfusions throughout the remainder of pregnancy and at delivery had 64,000 platelets, with the bleeding time 15 minutes.

A second full-term female infant, C. H., was born on April 24, 1945 (Chart 2). The baby's platelet count immediately after birth was 5,000; six hours later this dropped to zero, bleeding from the cord appeared, and petechiae were noticed over the body. Liver and spleen was not palpable. On the

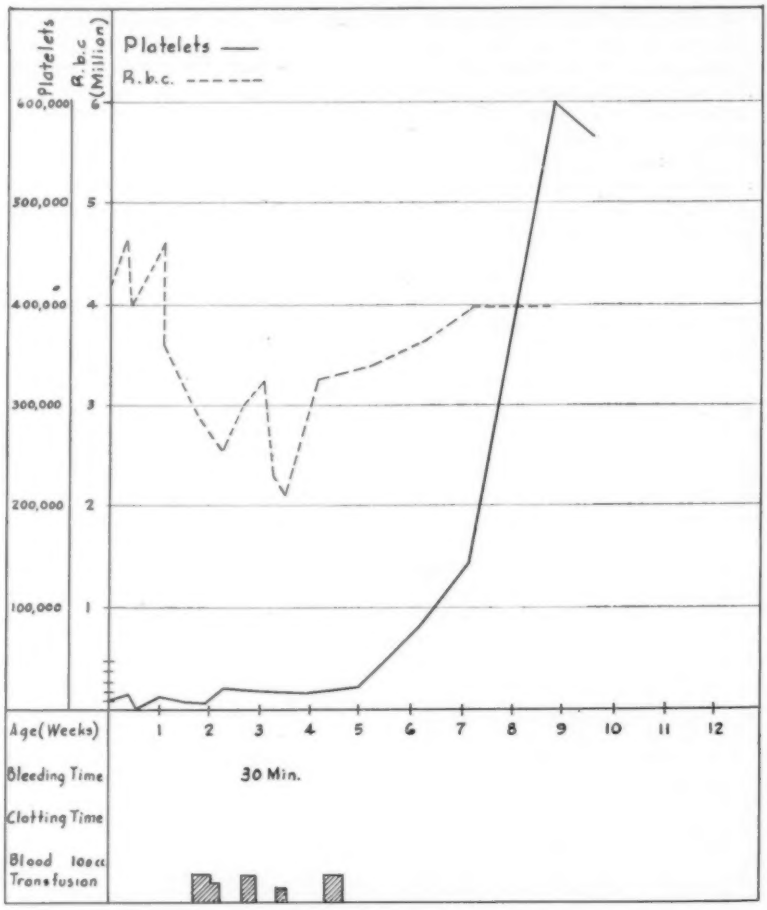

Chart 1.—D. H., March to May, 1941.

third day, blood appeared in the stools. At the age of one week, the platelet count remained at zero, bleeding time was 41 minutes, clotting time 15 minutes with no retraction, and blood was still present in the stools. During the second week the platelets began to increase spontaneously, the bleeding time decreasd, and no more bleeding tendencies were apparent. No transfusions were given until the baby was 5 weeks old; by this time the platelet count had risen considerably,

and two transfusions were then given because of anemia. This baby was discharged on June 25, 1945, at the age of 2 months, with 981,000 platelets. She was followed in clinic for the next three months, during which time she remained asymptomatic with a normal platelet count, and was seen again at the age of 16 months with no bleeding tendencies and a normal blood picture.

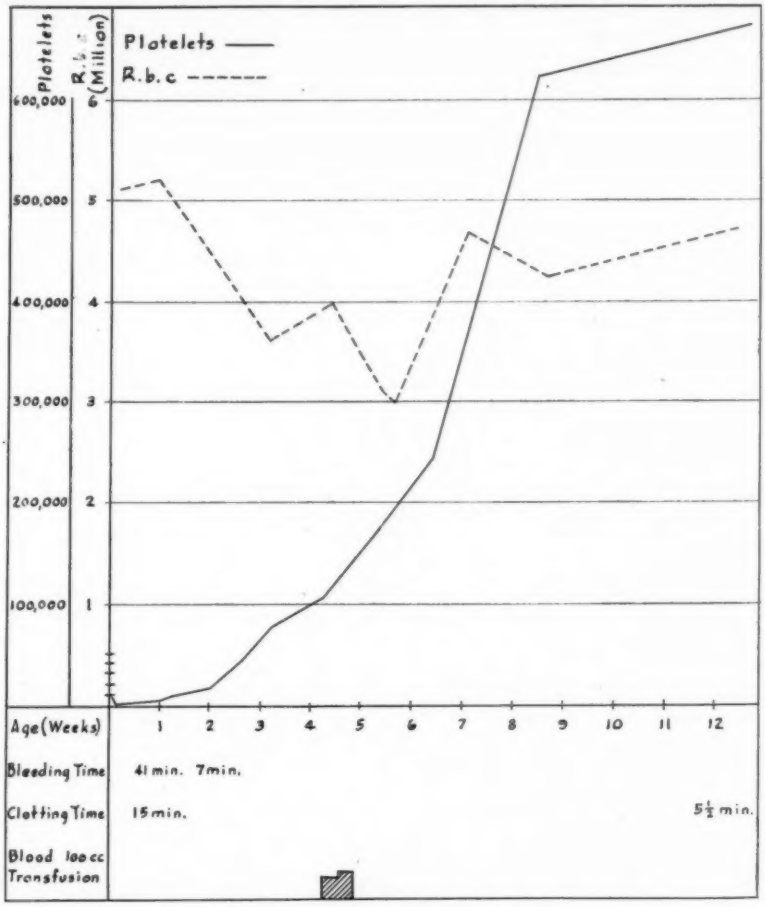

Chart 2.—C. H., April to July, 1945.

The mother's next admission to the hospital was on Aug. 20, 1946, with bleeding gums, petechiae, and 7,580 platelets. She had again been asymptomatic until the last half of pregnancy. A female infant, two weeks premature, was born on Aug. 21, 1946. Thorotrast study of the mother during this admission failed to reveal any accessory spleen.

This third child, S. H. (Chart 3), appeared normal at birth, but developed petechiae at the age of 2 days; platelet count was zero, bleeding time 62 minutes, clotting time 3 minutes, with no clot retraction; liver and spleen were not palpable. When the baby was one week old, the platelet count remained zero, the

bleeding time was still prolonged to 45 minutes with no clot retraction, and blood appeared in the stools. Tibial puncture, performed August 31, was followed by hematoma formation over the puncture site. The baby received transfusions every other day of life beginning on the second day, but there was no change in the number of platelets until she was 2 weeks old. From then on the platelets

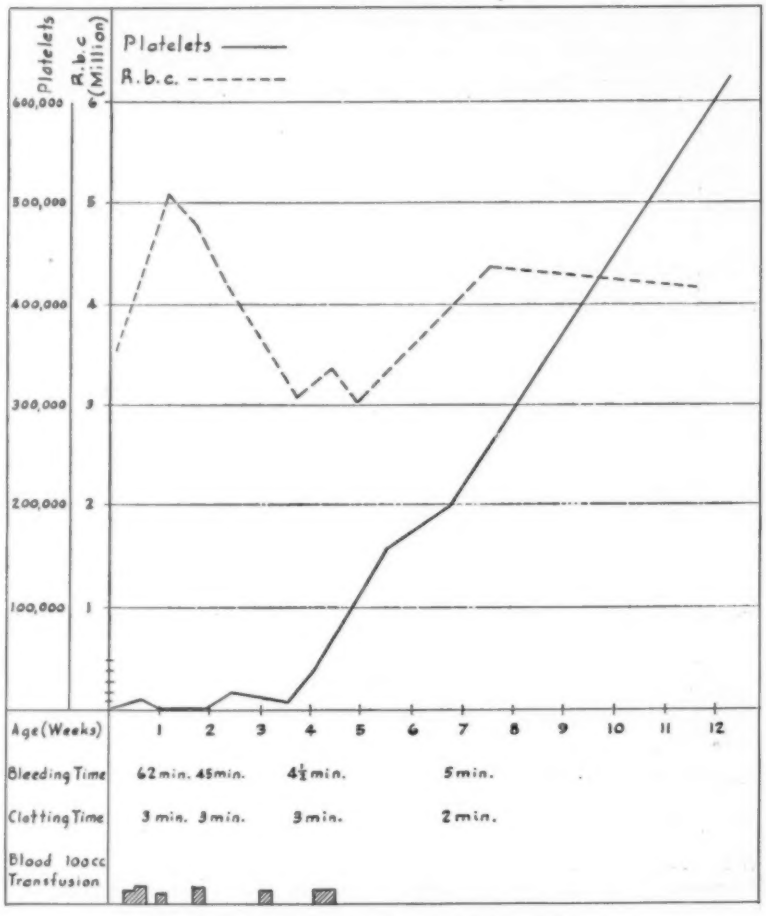

Chart 3.—S. H., August to November, 1946.

gradually increased, with diminishing bleeding time and disappearance of bleeding tendencies. She was discharged Oct. 17, 1946, at the age of 2 months, with 169,000 platelets, bleeding time 5 minutes, and clotting time 2 minutes, but still no clot retraction. On Nov. 12, 1946, she had 1,645,000 platelets, and there were no bleeding tendencies apparent.

SUMMARY

Congenital thrombocytopenic purpura has occurred as a familial condition in three successive children of a mother previously splenectomized for thrombo-

cytopenic purpura. In each of these children there has been a gradual spontaneous recovery to a normal blood picture during the first 2 months of life, and following recovery there has been no recurrence of thrombocytopenia up to the present time.

REFERENCES

1. Sanford, H. N.: Leslie, E. I., and Crane, M. M.: Congenital Thrombocytopenia, Am. J. Dis. Child. **51**: 1114, 1936.
2. Davidson, L. T.: Congenital Thrombopenia, Am. J. Dis. Child. **54**: 1324, 1937.
3. Whitney, L. H., and Barritt, A. S., Jr.: Spontaneous and Hereditary Thrombopenic Purpura in a Mother and Two Sons, Am. J. Dis. Child. **64**: 705, 1942.
4. Urbanski, A. X., and Hutner, C. I.: Thrombopenic Purpura Complicating Pregnancy, J. A. M. A. **120**: 754, 1942.
5. Morrison, M., and Samwick, A. A.: Congenital Essential Thrombopenic Purpura, Am. J. Dis. Child. **70**: 115, 1945.
6. Shefrin, A. E., and Schechtman, A.: Congenital Thrombopenia, Am. J. Dis. Child. **70**: 29, 1945.

American Academy of Pediatrics

Round Tables

Round Table Discussion on Infection in the Newborn Period

Chairman: Stewart H. Clifford, M.D., Boston, Mass.
Associates: Charles C. Chapple, M.D., Philadelphia, Pa.
G. D. Cummings, M.D., Lansing, Mich.
Katharine Dodd, M.D., Cincinnati, Ohio
Secretaries: Orville E. Barbour, M.D., Peoria, Ill.
Thomas P. Saltiel, M.D., Chicago, Ill.

CHAIRMAN CLIFFORD.—Infection is a greater hazard to the present generation of newborn infants than to their predecessors. Many factors have conspired to make this so—not only are more babies being born but they are being delivered in hospitals rather than at home and there has been possible no new construction of maternity hospitals to accommodate this increased patient load. There is also a great shortage of both trained nursing personnel and nursery attendants to care adequately for this huge hospital baby population. The resulting crowding and inadequate nursing care have provided conditions most favorable for the occurrence and spread of infection.

In this round table discussion it will be impossible to consider in detail all the types of infection that may affect newborn infants. The infections of the newborn infant that have much in common with those occurring in older infants will be treated in a superficial manner. The main purpose of this discussion is to consider the diagnosis, treatment, and prevention of those infections peculiar to the newborn infant, particularly those causing epidemic diarrhea. To be of value, the recommendations that come out of this discussion cannot be idealistic but must be practical and capable of accomplishment under existing conditions.

The infant may acquire a bacterial, parasitic, or virus infection from any one or more of several sources:

(1) Infection acquired from the mother either in utero or during the birth process.
(2) Infection acquired at short range by person-to-person transmission of pathogens through air-borne droplets.
(3) Infection acquired from pathogens present in the air.
(4) Infection acquired from physical contact with infected personnel or material.
(5) Infection acquired from the ingestion of pathogens contained in the food.

INFECTIONS ACQUIRED IN UTERO OR DURING THE BIRTH PROCESS

Studies on the mothers of infants with congenital chorioretinitis and other evidence of toxoplasmosis have revealed that six of seven mothers had toxoplasma neutralizing antibodies. This strongly suggests that the mothers were carriers of the parasite and that the parasite was capable of crossing the placental barrier.[1]

Recently, five cases of congenital malaria have been reported from Turkey, in all of which malaria plasmodia were demonstrated in the peripheral blood.[2]

It is well known that the virus of chicken pox and smallpox may pass through the placenta and infect the fetus. The effects of the rubella virus on the embyro have been given wide publicity in recent years. What effect other types of virus infections in the

[1]Heidelman, Joseph M.: Evaluation of Toxoplasma Neutralization Tests in Cases of Chorioretinitis, Arch. Ophth. 34: 28, 1945.
[2]Eckstein, A. and Nixon, W. C. W.: Congenital Malaria, Brit. M. J. 1: 432, 1946.

pregnant woman may have on the fetus is a matter of wide speculation but little factual knowledge.

Syphilis is the most important infection that the fetus may acquire from an infected mother. Dr. Dodd will give special attention to this subject.

In recent years we have observed three mothers with bacteremia or septicemia with infected infants at birth. The organism in one mother was the beta hemolytic streptococcus, her infant had the same organism on blood culture and a streptococcus pneumonia on post-mortem examination. Bacillus coli was the organism in the second mother; her infant had the same organism on blood culture. The third mother's organism was *Bacillus suipestifer;* her infant had a negative blood culture but a positive stool culture for this bacillus. A fourth mother in whom the result of a blood culture was not recorded had an infant with *B. suipestifer* on blood culture shortly after birth. This infant developed a *B. suipestifer* meningitis, from which he died.

There have been two infants who have developed meningococcus meningitis so shortly after birth that one assumes the infection was acquired in utero.

We have encountered a number of instances where the mother has developed an infected amniotic fluid, usually with *Bacillus coli,* and where the infant has been secondarly infected.

The possibility of the infant acquiring an infection during its passage down the birth canal is well known. Gonorrheal ophthalmia is one of the most common infections thus acquired. The infant may also pick up a monilia infection, and Dr. Dodd's recent work presents the disturbing possibility that the virus of epidemic diarrhea may be present in the vaginal mucosa.

INFECTIONS ACQUIRED BY PERSON-TO-PERSON TRANSMISSION OF PATHOGENS

The initial bacterial flora of the throat and nasopharynx is largely acquired through direct contact with adults.[3] The newborn infant may acquire an infection from an adult or infant carrying pathogens in his droplets. The most common organism thus transmitted are the *Staphylococcus aureus* and the streptococcus, although others may more rarely be involved. There is considerable evidence that this person-to-person contact is the most important method of spreading virus infection.

INFECTIONS ACQUIRED FROM PATHOGENS PRESENT IN THE AIR

The importance of air-borne pathogens in the development of infections in the newborn is difficult to evaluate. Infections of various types can undoubtedly occur by this route but they must be relatively rare.

INFECTIONS ACQUIRED FROM PHYSICAL CONTACT WITH INFECTED PERSONNEL OR MATERIAL

The infection of infants by direct contact with infected personnel or material is a very important type of infection. Infections of the skin, mucous membrane, and umbilicus are frequently of this origin. There is a strong suspicion that some varieties of diarrheal disease may be spread by infected nipples and rectal thermometers.

INFECTIONS ACQUIRED FROM THE INGESTION OF PATHOGENS CONTAINED IN THE INFANT'S FOOD OR FLUID

In general, the present methods of sterilizing infants formulae are very unsatisfactory. Recent studies of formula samples showed bacteria counts that would not have satisfied minimum marked requirements for raw milk. A large variety of organisms were recovered from the formulae, in some instances the bacteria were of the same species as those isolated from infants in the nursery as well as from the respiratory tracts or the stools of the personnel. The frequency with which Lancefield Group D streptococci were

[3]Torrey, J. C. and Reese, M. K.: Initial Aerolic Flora of Newborn Infants, Am. J. Dis. Child. 67: 89, 1944.

encountered in the throats of infants with epidemic diarrhea suggests infection by the fecal-oral route. Salmonella infection of the newborn is further evidence that poor technique may bridge the gap between the human intestinal tract and the infants.[4]

Syphilis in the Newborn Infant

Katharine Dodd, M.D.,* Cincinnati

At this point I would like to ask Dr. Dodd to discuss the subject of syphilis in the newborn, following which the rest of the time will be devoted to the problem of diarrhea in the newborn.

The incidence of syphilis in women of child-bearing age has been estimated as about 3 per cent, less than 1 per cent in white women of high economic status and more than 15 per cent in Negro clinic patients.[1] Of the pregnancies occurring in untreated syphilitic women, about 30 per cent will result in death of the fetus and perhaps 80 per cent of those born alive will be infected. If treatment is begun before the fifth month of pregnancy, only about 5 per cent of the offspring will have the disease; if after the fifth month, about 20 per cent. These are the figures given in the prepenicillin days. Early reports of the protection of the child as a result of treatment of the mother with penicillin during her pregnancy were even more encouraging. As more experience accumulates, one is forced to abandon some of the early optimism concerning penicillin as a quick sure-fire cure for syphilis in any stage of the disease. Whether or not the infant will be infected depends not only on the treatment the mother has received but also on the age of her syphilitic infection. Children born of untreated mothers whose syphilis was acquired at the time of conception or during the pregnancy will almost certainly be infected; those born of mothers with congenital syphilis or late latent syphilis will probably escape infection. In the year 1945, 1,870 women were delivered at the Cincinnati General Hospital. Of these, 1,003, or 53.6 per cent, were colored and 867 or 46.4 per cent white. Syphilis was diagnosed because of history or positive serology or both in 178 or 17.7 per cent of the colored women and 59 or 6.8 per cent of the white women. There were thirty more patients in whom the diagnosis of syphilis was doubtful. Twenty-nine of the babies born to the syphilitic women were stillborn. The other 208 became patients in the newborn nursery. The prenatal care given to the mothers varied all the way from excellent to none and the antisyphilitic treatment they had received varied from excellent to none. Many had been treated several years before the present pregnancy but had received no treatment during the pregnancy.

The diagnosis of syphilis in the newborn infant usually presents great difficulties. Clinical signs and symptoms are rarely present at birth. Serology of the mother just before delivery or of cord blood taken at the time of delivery is diagnostic in only about 60 per cent of the infants. They may have syphilis when the serology is negative and may be uninfected even though the serology is positive. Around the years 1933 to 1935 great reliance was placed on roentgenographic changes in the long bones at birth as evidence of syphilis. Ingraham[2] and others were apparently able to pick up by this means many cases of syphilis in infants a few days of age when all other signs were absent or equivocal. My experience both in Nashville and Cincinnati, unfortunately has not duplicated theirs. Only once have I seen a lesion which I thought was undoubtedly the result of syphilis in the roentgenogram of the long bones of a newborn child. That child's mother had been actively treated during the last month of pregnancy. The child's Kahn test, positive at birth, soon became negative and we could only conclude that the infant had probably been infected but had received sufficient therapy during intrauterine life to reverse the

[4]Rubenstein, A. Daniel, and Foley, George E.: Epidemic Diarrhea of the Newborn in Massachusetts, New Eng. J. Med. **236**: 87, 1947.

*From The Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

[1]Whipple, D. V., and Dunham, E. C.: Congenital Syphilis. I. Incidence, Transmission and Diagnosis, J. PEDIAT. **12**: 386, 1938.

[2]Ingraham, N. R., Jr.: Diagnosis of Infantile Congenital Syphilis During the Period of Doubt, Am. J. Syph. & Neurol. **19**: 547, 1935.

serology. As we have learned more about the roentgenographic appearance of long bones in conditions other than syphilis, we have become hesitant about the interpretation of minor or even major changes in the long bones. When the child has reached an age of 3 to 6 weeks and the roentgenogram reveals periosteal changes, irregular areas of decreased density at the ends of the long bones and especially an area of decreased density in the proximal, medial aspect of the tibia, syphilis seems to be the only diagnosis tenable. Other clinical signs of disease are by then almost always present. Repeated quantitative Kahn tests and repeated roentgenograms of the long bones combined with careful clinical observation will almost surely rule syphilis in or out by the age of 3 months. It is difficult to follow children this carefully, and even when it is possible one has lost the opportunity to begin therapy early.

The spread of syphilis through contact infection in the nursery rarely presents a problem. The question of treatment of a child who may or may not have syphilis is a problem. If the child has syphilis it is better to treat before signs and symptoms appear and before there is any danger of a fatal outcome because of overwhelming infection. In Cincinnati we try to weigh the infant's chances of infection, using the information we can obtain as to the age of the infection in the mother and the apparent adequacy of the treatment she has received. If the mother has received inadequate treatment, there arises the question whether the child has also received inadequate treatment by the absorption of drugs through the placental circulation. In the days when arsenic and bismuth were the antisyphilitic drugs of choice and one felt that adequate therapy meant at least a year and a half of continuous treatment, we treated only the occasional infant in whom a positive diagnosis could be made at birth. Now, we start penicillin injections if in our judgment there is as much as a 50 per cent chance of the infant's being infected. The child must be kept in the hospital after the mother leaves and has to be weaned from the breast, neither of which procedures we like. We do not know whether we have treated infants who were uninfected. As far as I know we have failed only twice to make a positive diagnosis when syphilis was present. Once the mother and child were discharged before the mother's Wassermann and Kahn tests had been reported and once the mother's Kahn test was reported as negative although she was infected. Before we adopted our present plan, three syphilitic infants had returned to the hospital with severe infection. One died in spite of therapy. The ideal way to deal with the problem of syphilitic infection in the newborn nursery is to prevent its occurrence by adequate care of the pregnant woman. That is a task for the obstetrician, the adult syphilologist, and the public health authorities. They should receive every encouragement from us. Meanwhile, the diagnosis and therefore the management of syphilitic infection continues to be a difficult problem in the newborn infant.

DISCUSSION

DR. J. C. JAUDON, ST. LOUIS.—When a diagnosis of syphilis is made, how is the infant treated?

DR. DODD.—At present we do not wait to make a definite diagnosis of syphilis but treat the child if we think he probably has syphilis. We are using intramuscular doses of penicillin given every three hours. The dose is 10,000 units every three hours for prematures and 15,000 units for full-term infants. We give a total of at least 1.6 million units to prematures and 2.4 million for full-term infants. It usually takes between fourteen and twenty-one days to complete the therapy.

DR. H. KENNEDY, JR., BIRMINGHAM, ALA.—Do you follow up the treatment with bismuth, arsenic, etc.?

DR. DODD.—We have not done so as yet but are just beginning to give bismuth and arsenic along with the penicillin.

DR. CLIFFORD.—What do you do if Wassermann or Kahn is positive after penicillin?

DR. DODD.—The Wassermann of the children who have negative tests before treatment has not become positive at completion of treatment. We follow these children with quantitative Kahn tests and use the criterion of a rise in titer or recurrent positive after we have negatives as evidence of relapse. None of our children have relapsed since we have used the larger dosage but most have not as yet been followed for a very long time. Most of the titers have ultimately become negative.

DR. CLIFFORD.—Is there a law in Ohio requiring a Kahn test on all pregnant women?

DR. DODD.—There has been one since November, 1945, but the law is not obeyed well and a good many of the women do not go to a doctor for prenatal care.

DR. R. A. HIGGONS, PORT CHESTER, N. Y.—In what length of time is the dosage given? How divided? How long do you stand pat on the treatment?

DR. DODD.—The first two parts of this question have already been answered. We have treated a few children a second time when the Kahn tests have been positive after nine months.

DR. CLIFFORD.—How valuable do you find the quantitative tests?

DR. DODD.—Quantitative tests done immediately after birth have not proved very valuable. We have had some babies with negative serology who have later developed syphilis. Unfortunately, most of the children have not been brought back until symptoms of syphilis developed, at which time the Kahn test has been strongly positive. Quantitative serology has apparently proved of value in following results of treatment. The children who have shown a steadily falling titer have so far stayed well. We really do not have enough cases to permit a very authoritative answer to this question.

DR. CLIFFORD.—The State should assume the responsibility of the follow-up observation of syphilitic infants. How would you regulate the treatment, Dr. Cummings?

DR. CUMMINGS.—Unless syphilitic infants can be followed by their own physicians, it would seem necessary to recommend that the follow-up become responsibility of the local health officer and his staff. Presuming that the initial treatment of the case was adequate, I would follow syphilitic infants clinically and by means of quantitative blood testing at periodic intervals. I believe it is the custom in the rapid treatment of adults to do a quantitative blood test once a month for six months, then once at the ninth month, once at the twelfth month, once at the eighteenth month and finally at the end of two years.

Epidemic Diarrhea of the Newborn Infant From the Point of View of the Clinical Investigator

Katharine Dodd, M.D.

By far the most serious infection which occurs in the newborn period is diarrhea. While the death rate for diarrhea in infants up to one year of age has been falling for the last 15 years and the death rate for infants under one month from all causes has also fallen, although at a slower rate, the diarrheal death rate for infants under one month has risen gradually during the same period. Epidemics of diarrhea occur in newborn nurseries in all countries. As visitors have come to us at the Cincinnati Children's Hospital since the end of the war, one of the most frequent questions has been, "What do you think is the cause of diarrhea of the newborn and what can be done to prevent it or treat it when it occurs?" Two visitors from foreign countries cited appalling figures of death rates from diarrhea of more than 30 per cent of the babies born in two large cities during a war year. In New York City, 9,236 newborn babies were reported to have been exposed to the disease by 1941.[1] Of these, 1,233 contracted the disease, a morbidity

[1]Frant, S., and Abramson, H.: Epidemic Diarrhea of the Newborn, in Brennemann's Practice of Pediatrics, Hagerstown, Maryland, 1945, W. F. Prior Company, Inc., v. 1, chap. 28, p. 19.

rate of 13.4 per cent, 540 of the babies died, a case fatality rate of 43.6 per cent, and a mortality rate of 5.8 per cent for the babies exposed. As one glances through medical journals one frequently comes upon a reference to an epidemic in one city or another. One of the last I noted was in the October issue of the *Journal of the American Medical Association*[2] where the following report from California appears under "Medical News." "On September 25 the Oakland Health Department closed and quarantined the maternity ward and nursery of the Providence Hospital in an effort to halt a mysterious outbreak of disease which has already killed six of seventeen babies afflicted with it since September 15. The disease has not been completely classified but its main symptom is diarrhea." In the first two years I was in Cincinnati there were three epidemics of diarrhea of the newborn as a result of which infants were admitted to the Children's Hospital. In one epidemic fourteen children came to our infant ward from one newborn nursery; all within a period of three days. A similar number were admitted to an improvised isolation ward in the hospital concerned. One-third of the children whom we cared for died. During the same two years three mild epidemics occurred in the newborn nursery of the Cincinnati General Hospital. None of the full-term infants was very ill but eight premature infants born in the same delivery room but cared for in a separate nursery by different personnel all contracted the disease and four of the eight died.

It is questionable whether epidemic diarrhea of the newborn constitutes a single entity. Bacteria present in milk, on the hands of nurses and doctors, or passed from mother to child during the process of birth or later may cause illness in which diarrhea is the chief symptom. In a recent epidemic[3] in Great Bend, Kan., involving twenty-four infants, nine of whom died, milk for 90 per cent of the community came from two dairies. On investigation it was found that the milk was inadequately pasteurized, contaminated after pasteurization, and sold in unsterilized bottles. Diarrhea was rampant throughout the town. Prior to every outbreak in the nursery, except one, a mother or nurse on the obstetric floor developed diarrhea. *Pseudomonas aeruginosa*, the organism which most of us know as *Bacillus pyocyaneus*, was apparently the causative agent of the diarrhea. It was isolated from two-thirds of the babies' stools and from the liver, spleen, and gall bladder of two infants on post-mortem examination. Various other organisms such as Salmonella and Proteus were found in some of the stools. It was thought that the babies acquired the infection from adults who cared for them rather than directly from the milk. This seems a shocking instance of what may happen when public health authorities become lax in these days when the public must rely on them for protection against contamination of both milk and water. It also sounds as if the technique employed in the hospital nursery must have been very poor. Cases of diarrhea in which pathogenic organisms have been isolated from the stools and at times from the blood stream have been reported from several other nurseries. Various types of dysentery bacilli and Salmonella, *Bacillus lactis aerogenes*, *Bacillus dispar*, and *Proteus morgani* have been some of the offenders. Interestingly enough, rarely did a real epidemic of diarrhea arise. Either the diarrhea concerned one baby when his mother also had diarrhea at the time of delivery or had organisms in her stools similar to those isolated from the baby. Sometimes one or more babies in adjoining cribs also became ill. However, according to one report[4] an entire nursery population of six babies contracted diarrhea due to a Salmonella organism. A nurse who was not ill but had the organisms in tremendous numbers in her stools was the probable source of infection. Four of the infants recovered and two died. In another epidemic[5] which concerned thirty-four infants, fourteen of whom died, *Bacillus mucosus*

[2]"Medical News," J. A. M. A. **132**: 399, 1946.

[3]Ensign, P. R., and Hunter, C. A.: An Epidemic of Diarrhea in the Newborn Nursery Caused by a Milkborne Epidemic in the Community, J. PEDIAT. **29**: 620, 1946.

[4]Abramson, H., Frant, S., and Oldenbusch, C.: Salmonella Infection of the Newborn: Its Differentiation from Epidemic Diarrhea and Other Primary Enteric Disorders of Newborn, M. Clin. North Am. **23**: 591, 1939.

[5]Jampolis, M., Howell, K. M., Calvin, J. K., and Leventhal, M. L.: Bacillus Mucosus Infection of the Newborn, Am. J. Dis. Child. **43**: 70, 1932.

was thought to be the causative agent. The organism was cultured from the stools and from the throats of three nursemaids. No further cases occurred after their removal from the nursery. *B. dispar* was recovered from the stools of thirty-six infants in an epidemic reported by Schwentker[6] in Baltimore. Unfortunately, no details of the epidemic are given except for the fact that twenty-one of the infants died.

A recent survey of epidemic diarrhea of the newborn in Massachusetts[7] revealed many inadequacies in nursing care in nineteen epidemics studied. Overcrowding, insufficient personnel, general use of a common thermometer, and inadequate supervision of fromula making were frequently encountered. Laboratory examinations of sterilizing solutions, including alcohol hand solution and thermometer dips, formulas, and nipples showed heavy bacterial contamination. Nevertheless, no particular pathogenic organism was consistently isolated from the babies' stools in any of the epidemics. Similarly, no pathogenic bacteria have been demonstrated by most careful bacteriological technique in most instances where the outbreak of diarrhea has been widespread. The infant's stools, nasopharynxes and blood, the nasopharynxes and stools of all attendants, the bottles, nipples, and milk used in formula feedings, have often all been cultured but only the usual bacterial flora found. At times it has been suggested that organisms, such as colon bacilli, which are nonpathogenic for adults might be pathogenic for infants who have as yet acquired no immunity to them. If this were true it would be difficult to explain why a large number of babies in a nursery should suddenly develop diarrhea whereas at another time no diarrhea occurs in spite of the fact that the same type of organisms are present in the babies' stools at both times. Epidemic diarrhea must be caused by an infectious agent present at some times, absent at others and capable of spread from infant to infant by one means or another.

The symptomatology of diarrhea of the newborn has usually varied little from one epidemic to another. Breast- and bottle-fed babies are attacked equally. The incubation period usually appears to be short, a matter of four days or less. Occasionally an infant has diarrhea almost from birth. At the outset of an epidemic the infants usually begin to have loose stools on the third day—the time when loose stools transitional from meconium to fecal stools may well be a normal finding. For this reason the abnormal stools are often ignored until the infants begin to look ill or diarrhea develops in older infants who had previously been doing well. Sometimes, particularly now when many obstetrical patients are discharged from the hospital on the fourth or fifth day after delivery, the first intimation that there is an epidemic of diarrhea comes when several babies recently discharged from a nursery develop diarrhea at home. The diarrheal stools number from three or four to nine or ten a day. They are usually green and watery and are expelled with explosive violence. Some authors have emphasized the absence of mucus and blood, but it has been my experience and that of some others that the stools often contain large amounts of mucus and may at times be streaked or flecked with blood. Occasionally the stools are not loose but are heavily blood streaked. In a severe epidemic dehydration, acidosis and listlessness follow closely upon the heels of the diarrhea. The infants refuse to nurse and may vomit. As the disease progresses otitis media, pneumonia, or even septicemia caused by secondary invaders may develop. Post-mortem examination of fatal cases reveals slight pathological changes. There are often congestion and swelling of the small bowel, especially of the jejunum and ileum. Occasionally small, shallow ulcers are seen. On microscopic examination there is congestion of the mucosa and submucosal bed with edema of the submucosa. Widely scattered small foci of necrotic cells may be noted as well as small areas of hemorrhage just beneath or upon the mucosal surface. There is usually a slight polymorphonuclear leucocytic infiltration of the submucosa. No intracellular inclusions have been noted. In infants dying late in the disease bronchopneumonia is often found.

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[6]Schwentker, F. F.: Dysentery Due to Bacillus Dispar, Am. J. Dis. Child. **50**: 1321, 1935.

[7]Rubenstein, A. D., and Foley, G. E.: Epidemic Diarrhea of the Newborn in Massachusetts, New England. J. Med. **236**: 87, 1947.

A virus etiology for most epidemics of the disease has been suspected for the last ten years. Lyon and Folsom[8] described three epidemics which occurred at a time when clinical influenza was unusually prevalent in the community and suggested that the malady was an expression of infection with the influenza virus in the newborn. Light and Hodes[9] in 1943 reported the first apparently successful isolation of a filterable virus from stools collected from infants in four separate epidemics of varying severity. Calves were injected intranasally with Seitz filtrates of the stools. A bloody mucoid diarrhea ensued in two to five days. The con stitutional reaction was, as a rule, minimal. The disease was relapsing in nature and lasted from eight to fifty-four days. Successive calf passage was readily accomplished with both filtered and unfiltered material. Following recovery, large doses of active material failed to cause disease. Cross-immunity studies indicated that the four strains were apparently identical. Sera obtained from six babies following convalescence conferred complete or partial protection from intranasal infection of the animals. It was thought that a somewhat similar diarrheal disease indigenous to calves and caused by a virus was ruled out as the etiological agent of the disease in the calves studied.

Buddingh and Dodd[10] were able to produce lesions on the scarified cornea of rabbits with an inoculum of stool obtained during an epidemic of diarrhea in one of the nurseries for newborn infants at Vanderbilt. The agent was readily filterable through Berkfeld V candles. Similar lesions of the cornea had been produced earlier with swabbings from the mouth and stools of older infants with a mild stomatitis and diarrhea. Within twenty-four hours of inoculation haziness with cloudy opacity developed along the lines of scarification of the cornea; hyperemia and swelling of the conjunctiva, and in many instances an intense iritis developed. The reaction persisted for about forty-eight hours. Microscopic sections showed nonspecific congestion, edema, and infiltration with polymorphonuclear cells. Strains of the agent were maintained for as many as forty-five serial passages. Immunity developed in the rabbit eye in a period of three weeks. Serum obtained from twelve patients during the acute disease failed to prevent a reaction in the rabbit cornea when mixed with virus; similar mixtures using serum obtained during convalescence produced no lesion. Attempts to propagate the virus in other animals or in the developing chick embryo have so far been unsuccessful. The filterable agent has been isolated by Buddingh from stools obtained from epidemics in Nashville, Memphis, Cincinnati, and Boston. Cross-immunity has been demonstrated between all strains regardless of whether the death rate in an epidemic was none or over 50 per cent. It has not been possible to test whether the two viruses isolated by Light and by Buddingh are the same. It seems probable that a virus is the usual etiologic agent in epidemic diarrhea of the newborn but it may be that, as in encephalitis, different viruses are concerned in different epidemics.

Until the etiologic agent of diarrhea of the newborn can be readily demonstrated, the mode of spread will remain difficult to establish. The usual method of dealing with an epidemic is to quarantine the nursery and often the maternity ward as well. In the meantime the babies are cared for in the quarantined nursery, transferred to the infants' or children's wards in the same hospital, or admitted to other hospitals in the city. I should like to interject a word of caution concerning the last two procedures. Frant states in an article in Brennemann's Pediatrics that no adult in contact with babies suffering from diarrhea of the newborn has contracted the disease nor have there been any cases among older infants and children in the open pediatric wards in which these children were cared for. This has not been our experience either at Vanderbilt or in Cincinnati. In the first nursery epidemic studied by Buddingh and Dodd, mouth swabs from three of the four nurses in charge of the nursery were found to produce a typical reaction in rabbit eyes. One of the

[8]Lyon, G. M., and Folsom, T. G.: Epidemic Diarrhea of the Newborn; Clinicoepidemic, Pathologic and Therapeutic Aspects, Am. J. Dis. Child. 61: 427, 1941.

[9]Light, J. S., and Hodes, H. L.: Studies on Epidemic Diarrhea of the New-born; Isolation of the Filterable Agent Causing Diarrhea in Calves, Am. J. Pub. Health 33: 1451, 1943.

[10]a. Buddingh, G. J., and Dodd, K.: Stomatitis and Diarrhea of Infants Caused by Hitherto Unrecognized Virus, J. PEDIAT. 25: 105, 1944.

b. Buddingh, G. J.: Virus Stomatitis and Virus Diarrhea of Young Children, South. M. J. 39: 382, 1946.

nurses apparently carried the infection home to her 6- and 8-year-old daughters. Four other adults who were subsequently in close contact with infected infants developed a mild stomatitis which was proved to be positive for the virus. In every instance infants of varying ages cared for by these four individuals became ill with diarrhea. When newborn infants with diarrhea have been admitted to the infant ward either at Vanderbilt or Cincinnati, secondary cases of infection have always developed on the ward in infants varying in age from a few days up to at least 6 months. Premature infants cared for in a separate, well-isolated nursery but attended by the same doctors and nurses as the sick infants, have developed diarrhea even though they were often a month or two old at the time of exposure. The disease has been severe in the premature infants and the fatality rate is usually high.

Because the first cases in a nursery have often developed in babies of 2 to 3 days of age, we thought that the babies might be acquiring their infection during passage through the birth canal. In thrush and inclusion blennorrhea, infection is known to occur in this manner. In many of the reported instances of diarrhea of the newborn infant caused by pathogenic bacteria, infection was almost certainly acquired during the birth process. With the possibility in mind that the mother might harbor the virus infection in her vagina, swabbings were obtained from the mouth and stools of the infant and from the vagina of the mother when diarrhea developed in the newborn nursery in Cincinnati. The swabs were sent to Dr. Buddingh by air mail. Virus was isolated on rabbit corneas from the material obtained from both mother and child and identified by cross protection tests. If the birth canal of the mother should prove to be a common source of infection for the infant, the prevention of diarrhea in nursuries will indeed present a difficult problem. Small nursery units, extreme care in hand washing and precautions against contamination with mouth secretions may prevent wide dissemination of infection but single cases will continue to occur unless by some miracle an antibiological can be found which will prevent virus infections. Immune globulin may prove of some value in the prevention of infection. The initial trial by High, Anderson, and Nelson[11] did not lead to beneficial results.

My experience in many different newborn nurseries is not wide. I have never seen a serious epidemic develop in a nursery where the babies were carefully watched by pediatricians even though the physical facilities except for the presence of plenty of soap and water for hand washing were poor. The serious epidemics I have seen have arisen in nurseries where the babies were cared for by doctors whose interest was primarily in the mother rather than the infants. In the most serious epidemic I saw the story as given by the parents was, "We thought the baby was doing well, but on the way home he had four or five loose, watery stools and has continued to have diarrhea ever since." Surely some of the diarrhea must have developed before the babies left the hospital but was unnoticed in the busy, overcrowded nursery. Three epidemics reported from the New York Hospitals[12] where the infants are carefully watched by pediatricians, carried a very low death rate—none except among premature infants. Perhaps I have just been fortunate, and next week or next month severe diarrhea will strike in the nursery at the Cincinnati General Hospital where the babies are seen daily by the pediatricians and in spite of overcrowding and poor physical facilities hand washing is rigorously carried out. I should like to believe that disastrous epidemics will not occur while we adhere to our present watchfulness and techniques.

The treatment of diarrhea requires, I am sure, as well or better trained personnel than does its prevention. Some infants continue to nurse and gain well in spite of the passage of an increased number of somewhat watery stools containing large amounts of mucus. Such infants should be carefully watched but their food and fluid intake left undisturbed. Others, the premature infants in particular, rapidly develop the same dehydration, acidosis, apathy or restlessness that occurs in all severe diarrheas of infancy. They must receive a course of carefully planned and carefully executed therapy. Opinions differ as to how long infants

[11]High, R. H., Anderson, N. A., and Nelson, W. E.: Further Observations of Epidemic Diarrhea of the Newborn. I. Observation of a Biphasic Type of Clinical Course. II. Therapeutic Measures Including Prophylactic and Therapeutic use of Gamma Globulin, J. PEDIAT. 28: 467, 1946.

[12]Baker, C. J.: Epidemic Diarrhea of the Newborn, J. PEDIAT. 14: 183, 1939.

with diarrhea should be starved, what amounts of normal saline, glucose solution, and whole blood and plasma, or at times solutions of casein hydrolysate should be administered and in what order they should be given. Perhaps by now the role of potassium-containing solutions in the treatment of diarrhea is more thoroughly evaluated than it was last year and they too should be used in therapy. In spite of occasional favorable reports of the influence on mortality figures of various chalk and apple mixtures it is difficult for me to believe from my experience or knowledge of diarrhea in the newborn that these remedies can exert any favorable influence on the primary infection. In spite of some favorable reports on the use of various sulfonamides, I doubt if they exert any influence on the course of the diarrhea except in the rare instances where diarrhea is caused by bacteria which are sensitive to sulfonamides.

Our plan of therapy in Cincinnati is to stop all oral intake in the dehydrated infants and treat by means of parenteral fluid intake. Information on electrolytes and total osmotic equilibrium is obtained by means of carbon dioxide, chloride, and nonprotein nitrogen determinations. Initially, in order to avoid embarrassment of the circulation of severely dehydrated patients by the use of hypertonic solutions, 50 to 100 c.c. of physiological saline are administered rapidly. The acidosis is then corrected by not more than twenty volumes per cent by the administration of 3.7 per cent sodium bicarbonate solution. In patients with moderate acidosis sodium lactate is often used. In the first twenty-four hours saline containing fluids in amounts equal to 5 to 10 per cent of the body weight in addition to the basal requirement of 100 to 150 c.c. is given. The total fluid requirement for twenty-four hours of 150 c.c. per kilogram of body weight is made up by the use of 5 per cent glucose in 100 to 300 c.c. amounts administered alternately with the saline in order to spread the electrolyte administration evenly throughout the day. In most cases, blood, plasma, casein hydrolysates, and hypertonic solutions of glucose or glucose in saline are used only when dehydration is largely overcome. In cases of severe circulatory collapse or anemia blood and plasma are occasionally given in the first twenty-four hours. The intravenous infusion is continued until the infant is well hydrated and the diarrheal stools have ceased or at least greatly lessened in frequency and water content. While the diarrhea continues, one and a half of two times the basal amount of electrolyte is supplied as normal salt solution or the saline contained in blood or plasma. The infants are carefully watched for the appearance of edema, the recurrence of diarrhea, and the development of any untoward symptoms. Chemical checks of the chloride, carbon dioxide, nonprotein nitrogen and protein content of the plasma are made as indications arise. Because we have found that hypocalcemia with symptoms of tetany often develops during the postacidotic phase, the serum calcium is also determined if the baby becomes irritable, unduly drowsy, or has symptoms of collapse or convulsions. A dilute solution of calcium chloride is given by gavage, or in desperate cases dilute calcium gluconate or calcium chloride by vein when such symptoms occur. We think the administration of calcium has been lifesaving in many instances.

No exact rules are followed as to resumption of feedings. We prefer when possible to delay oral intake until the diarrhea has ceased and to start the feedings while the intravenous infusion is still in place. We usually begin with 15 to 30 c.c. of water or glucose in water to avoid aspiration pneumonia in case the baby vomits. If this is well taken, equal amounts of an easily digested formula such as skimmed or half skimmed milk and sugar is offered. The amount is gradually increased, the baby's fluid and electrolyte requirement being made up by the continuing intravenous infusion or by the use of subcutaneous fluids. Sulfadiazine is usually administered for the first few days until it is established by culture that there are no dysentery organisms in the stools. Penicillin injections are given at the least suspicion of secondary infection but are not used routinely. As diarrhea of the newborn has a tendency to relapse one sometimes has to stop all feedings and start treatment again from the beginning. We have fortunately not had the opportunity to treat a large number of babies from a severe epidemic since the adoption of all the details of our plan but feel fairly confident that if fourteen more babies should arrive on our ward as sick as these we saw nearly two years ago we could now save more than two-thirds of them.

Epidemic Diarrhea of the Newborn from the Point of View of the Epidemiologist and Bacteriologist

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The material to be presented here was gathered by the Diarrhea and Enteritis Study Group of the Michigan Department of Health Laboratories. This study group was organized four years ago for the specific purpose of attempting to determine the etiology of the clinical entity known as epidemic diarrhea of the newborn. The group was financed jointly by the Kellogg Foundation and the Michigan Department of Health Laboratories.

Study personnel were organized into two integrated units. One unit was composed of physicians, nurses, and clerks for the purpose of studying hospital outbreaks. The other unit was composed of laboratory personnel for the purpose of analyzing the various specimens collected by the medical group.

During the first year of the program it became evident that the group would be called upon to study a wide variety of outbreaks, some involving newborn nursery patients; others involving pediatric patients.

It soon became evident also that the study of infants suffering from the various types of gastroenteritis should be paralleled by a study of a normal newborn population. Accordingly, arrangements were made with a local general hospital whereby the study group could collect certain data on normal newborn infants. This latter study was responsible for the ultimate interest of the study group in nursery techniques, and for the position the group now takes on the subject of infection control in nurseries.

This discussion will be limited largely to studies on the etiology of the various types of infant gastroenteritis and to studies on methods for preventing or controlling nursery infection.

STUDIES ON ETIOLOGY

The epidemics studied by our group can be classified into three categories:

a. Epidemics caused by various members of the Salmonella group.

b. Epidemics of true epidemic diarrhea of the newborn.

c. Epidemics with no clear-cut etiology.

Salmonella Outbreaks.—The wide interest in the etiology of epidemic diarrhea of the newborn has, in a way, served to obscure the importance of the Salmonella group in infant gastroenteritis. This has been particularly true in the smaller hospitals where adequate laboratory facilities were not available. We have observed one nursery outbreak caused by *Salmonella panama* and a number of pediatric outbreaks caused by various members of the Salmonella group.

The *S. panama* outbreak was observed in a nursery in a Michigan hospital in March, 1944. The first cases observed were cases of meningitis and not of diarrhea. The assistance of the Department of Health was requested on the basis of the meningitis. A careful study of the situation revealed both meningitis and diarrhea occurring in the same infants. It also became obvious that diarrhea, meningitis or both had been observed sporadically for the previous six months. Local reports were that diarrhea had been rampant six months prior to the investigation. Autopsy material from three deaths, which occurred in March, yielded *S. panama* in blood, spinal fluid, meninges, lung tissue, and feces. *S. panama* was also recovered from the stools of our graduate nurse, one nurses' aide and one maid. In addition, the organism was recovered from eight well newborn infants and two well mothers of these infants. Altogether, twelve infant deaths could be attributed to this organism. *S. panama* was isolated from the stools of two other infants hospitalized in two other cities. Investigation revealed that these infants were born in the hospital under investigation. The outbreak was brought to a close by the removal of the carriers among the personnel. It is interesting to note that every strain of *S. panama* which we have isolated since this outbreak in 1944 has come from an individual having his origin in the city in which the nursery outbreak occurred.

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More recently we have had an opportunity to observe two cases of *Salmonella typhimurium* in infants in a pediatric section of a general hospital. One of these infants was admitted as a boarder and the other with a possible case of pyloric stenosis. The first infant had two distinct episodes of diarrhea with elevated temperatures, the first occurring about five weeks after admission. Following the second episode, a stool examination revealed *S. typhimurium*. The organism has remained present in the stools to the present time, or a period of approximately ten weeks. The second patient was placed in the same room with this patient about the time the laboratory began to report not *S. typhimurium* but *Salmonella typhimurium var. copenhagen*. Two weeks after admission, the second patient had a mild episode of diarrhea and the laboratory reported *S. typhimurium var. copenhagen* as present in the stools. The second patient was clearly a victim of cross-infection, since his admission stool had been negative. The stools of these infants still contain, *S. typhimurium var. copenhagen* at the present time, although both infants are clinically free from diarrhea. A stool survey of pediatric nurses revealed one nurse whose stool contained *S. typhimurium* and who reported a previous episode of diarrhea.

This type of small outbreak has been observed rather commonly and emphasizes the necessity for carrier control among hospital personnel.

Epidemic Diarrhea of the Newborn.—A number of outbreaks of true epidemic diarrhea of the newborn have been observed and two are worthy of mention.

The first outbreak occurred in the premature section of a children's hospital. This outbreak occurred at a time when it was impossible to obtain newborn calves for experimental use after the method of Light and Hodes.[1] As a result, material obtained from infants was tested only in the smaller laboratory animals. The rabbit corneal test was also included, based upon the work of Buddingh and Dodd[2] in the realm of stomatitis and diarrhea, although none of the infants exhibited a clear-cut stomatitis. All of the animals tested were negative but the corneal test revealed some interesting findings. Seitz filtrates of pools of infant stools gave positive eye reactions as described by Buddingh and Dodd. Subsequent experience with serial passages of corneal material, however, led us to believe that the test was erratic if not nonspecific. As a result, a large number of rabbit corneas were tested with trauma, trauma and alundum, stools from normal infants, normal infant mouth washings, strains of Monilia, coagulase positive staphylococci, hemolytic streptococci and coliform organisms. It was possible with all of these specimens or techniques to produce what we considered to be typical positive reactions as described by Buddingh and Dodd. We were unable also to obtain consistently positive eye reactions on serial passage with stool material from infected infants or from control material. Our conclusion at the end of a series of experiments which involved 1,500 rabbits was that the rabbit corneal test was nonspecific unless it could be confirmed by the presence of intracytoplasmic or intranuclear inclusion bodies.

We were, therefore, unable to isolate a specific etiologic agent in this outbreak.

One interesting clinical observation was made. The study group assisted the hospital in establishing new techniques in the reopened nursery. The chief nurse of the study group acted as supervisor of the premature nursery for a period of twelve weeks. This period of time was selected because there had been three consecutive outbreaks all of which appeared approximately six weeks following each reopening. Over the period of twelve weeks there were no new cases of epidemic diarrhea of the newborn. However, on two adjacent wings on the same floor there developed nine and nine cases, respectively. These cases, however, developed in infants older than one month of age. There were no positive laboratory findings and the clinical picture was that of epidemic diarrhea of the newborn. Because the generally accepted definition of epidemic diarrhea of the newborn limits the disease to neonatal infants, these cases were classified as house or endogenous diarrheas.

The second outbreak occured in the smaller of two nurseries in a general hospital and involved twenty-two babies. Test material was obtained during the first twenty-four hours

[1]Light, Jacob S., and Hodes, Horace L.: Studies on Epidemic Diarrhea of the Newborn: Isolation of a Filtrable Agent Causing Diarrhea in Calves, Am. J. Pub. Health 33: 1451, 1943.

[2]Buddingh, G. J., and Dodd, K.: Stomatitis and Diarrhea of Infants Caused by a Hitherto Unrecognized Virus, J. PEDIAT. 25: 105, 1944.

and before therapy was begun. Nose, throat, and stool specimens obtained were free from bacterial pathogens. Pooled material was tested for viruses in mice, monkies, guinea pigs, baby chickens, cotton rats, chick embryos, hamsters, newborn pigs, and newborn calves. This one experiment involved approximately 1,500 animals. All of the animals or media reacted negatively except the calves. The first passage included four test calves and four control calves. The four test animals came down with diarrhea in one to three days and were acutely ill. Stools were watery yellow in character and occasionally contained flecks of blood. All of the control animals remained well. Stool material from the four infected animals was subsequently passed through five serial passages in calves with the production of diarrhea. The sixth and subsequent passages, however, failed to produce diarrhea and the agent involved either lost potency or was lost in passage. Inocula included unfiltered stool suspensions, Seitz filtered suspensions, and ultracentrifuged bacteria-free suspensions. The agent causing the calf diarrhea, therefore, appeared to be filtrable. We were satisfied in this single experience that we were dealing with a filtrable agent of the type described by Light and Hodes although we were unable to maintain the potency of this agent.

It is interesting to note that of the twenty-two babies involved in this outbreak, four also had impetigo, two conjunctivitis and one had an upper respiratory infection.

Epidemics with no Clear-cut Etiology.—A number of outbreaks of neonatal diarrhea were observed which could not be called clinical epidemic diarrhea of the newborn and which were not caused by any well-defined pathogen. These outbreaks were usually mild in type, explosive in onset, short in duration, and without fatalities. Daily stool totals were usually not markedly increased and stools were semiliquid-green in character rather than liquid yellow. Nose, throat, and stool specimens were negative for the accepted bacterial pathogens. It was customary, however, to isolate a variety of organisms from these specimens which aroused considerable speculation as to their etiologic significance. This group included coagulase positive staphylococci, hemolytic streptococci, various strains of Proteus, *Salmonella alkalescens, Bacterium alkaligenes* and various coliform organisms. These organisms were also routinely recovered from the various supplies, equipment, and solutions of the nurseries. In one nursery, for example, *B. alkaligenes* was isolated from twenty-four infant stool specimens, fifteen meconium specimens, one infant nose specimen, three nurse stool specimens, and three nurses' aide stool specimens. It was also isolated from nursery basins, enema solutions, subcutaneous saline solutions, soap solution, table tops, and hand brushes.

It has gradually become the opinion of the study group that this type of outbreak is due to massive bacterial contamination with organisms usually considered to be of low or absent pathogenicity, together with a complete absence of the usual nursery techniques. It is felt that filth in the nursery is the principal contributing factor.

STUDIES ON METHODS FOR PREVENTING NURSERY INFECTION

As a preliminary to the study of these infants, it was necessary to standardize nursing techniques, especially those relating to infection control. The term technique was defined broadly in order to cover all of the potential routes of infection to the nursery population. An attempt was made to visualize all of the possible infection routes and then to establish the proper barriers to these routes outside the physical units containing the infant population. As a result, emphasis was placed on the following points:

1. *Expert Nursing Supervision.* Four specially trained graduate nurses were placed in charge of the nursery, one acting as general supervisor. It was felt that the entire success of the project would depend on these nurses and subsequent experience confirmed this opinion.

2. *Adequate Nursing Personnel.* Student nurses were assigned to the nursery in a ratio of one nurse for every eight mature infants and one nurse for every four premature infants. This ratio has been rigidly maintained over the four-year period.

3. *Infection Control Among Nursery Personnel and Mothers.* Each shift supervisor was assigned the responsibility for determining the presence of infection among nurses and mothers. Nurses were questioned directly regarding upper respiratory infection or diarrhea. No nurse was permitted to go on duty following a report of any type of infection. The gen-

eral supervisor questioned the mothers daily for the presence of infection. When infection was evident, babies were placed on bottle feeding only or placed in isolation if continued at the breast. In short, a definite effort was made to prevent individuals with frank infection from actually contacting the infant population.

4. *Carrier Control Among Nurses and Mothers.* Nose, throat and stool specimens were collected from nursery personnel monthly and from mothers at admission. It was felt that this was a particularly important procedure in view of the rather high incidence of Salmonella infections in adults.

5. *Formula Sterilization.* It was decided to steam sterilize all formulas, except those containing lactic acid. Formulas were sterilized as integrated units, that is, the bottle containing the formula was nippled and covered at the time of sterilization. Formulas were then autoclaved at 121° C. for eight minutes. This sterilization period was determined by laboratory tests for sterility.

6. *Daily Rounds on Infants.* The general supervisor was assigned the responsibility of observing each infant at bathing time for abnormal signs and for charting suspicious signs accurately. It was felt that the supervisor, by this method, would have the best opinion on the condition of each infant.

7. *Isolation of Infected Infants.* Infants with obvious signs of infection were immediately isolated. Infants with four or more abnormal stools in twenty-four hours were also isolated. Skin lesions were inspected carefully and infants with as few as one or two true pustules were also placed in isolation.

8. *Hand Technique.* Hand technique in the nursery was rigidly enforced. Each nurse was expected to wash her hands carefully with soap and running water after each baby and between each baby and contaminated objects. Each nurse and all other individuals entering the nursery were required to scrub hands and arms for five minutes with a brush, soap, and running water, and to wear sterile caps, masks, and gowns.

9. *Charting.* The general supervisor was required to insist on accurate charting. It was appreciated that accurate charting is of real value in determining the presence of an epidemic.

10. *Cleanliness.* Absolute cleanliness was insisted upon and it was required that the nursery be kept clean by wet mopping and dusting. Contact points where infants might become infected were cleaned with germicidal solutions.

11. *Sterile Supplies.* All linens and other supplies not affected by steam were sterilized for one hour at 121° C.

12. *Visitor Control.* Visitors were limited to two grandmothers and the father. By this method, the variety of outside adult contacts to the mother and baby was markedly reduced.

Once this general plan was in operation, an attempt was then made to evaluate the influence of this plan, if any, on the incidence of infection in the infant population. Each infant was observed daily for evidences of infection. A nose, throat, and stool specimen was taken routinely on each infant on the first day of life and every three days thereafter during his nursery stay. All suspicious skin lesions and eye drainages were cultured. The ultimate objective was to attempt a correlation between technique on the one hand and clinical and laboratory findings on the other. After fifteen months of experience a correlation was attempted between the incidence of all types of clinical infection and positive laboratory findings on fourth-day infant stools. The fourth day stool was selected to avoid culturing meconium specimens and to cover the greatest possible total of babies. Stools were called positive when they contained coagulase positive staphylococci, beta hemolytic streptococci and the accepted enteric pathogens of the Salmonella and Shigella groups. The only pathogenic organism recovered in the fifteen-month period was the coagulase positive staphylococcus and there appeared to be a close correlation between the presence of this organism and the amount of clinical infection. Thus, at the beginning of the period there were forty-three cases of clinical infection and fifty-seven staphylococcus positive stools. Fifteen months later there were seven cases of infection and one staphylococcus positive stool in an

equivalent population. It therefore appeared that the program was having some influence on the reduction in the number of cases of all types of clinical infection and likewise on the reduction of bacterial pathogens present as observed in the stools. The average case rate and the average positive stool rate have remained at a very low level up to the present time. No cases of epidemic diarrhea of the newborn were observed over the four-year test period nor were any cases of Salmonella or Shigella infection observed. The type of impetigo now present is markedly different than that seen at the beginning of the four-year period. Four years ago, an infant with impetigo would generally be covered with lesions. At the present time the vast majority of infants classified as cases of impetigo have only a small number of lesions, usually localized in one skin area. There has been a general decline in all of the types of nursery infection ordinarily observed. This four-year freedom from the diarrheal diseases seems rather remarkable in view of the fact that this nursery had experienced three consecutive outbreaks of epidemic diarrhea of the newborn in the three years prior to the beginning of the study. On the basis of this four-year experience it seems possible to draw certain tentative conclusions. These are:

1. It is possible to establish a workable pattern of technique which has as its objective the reduction or elimination of nursery infection.

2. This technique appears to be responsible for the reduction in the incidence of neonatal diarrhea and the reduction in the incidence of other nursery infections.

3. This technique also appears to be responsible for a reduction in the incidence of pathogenic bacteria observed in the stools of normal infants.

No attempt has been made as yet to evaluate individual nursery procedures in relation to infection control. It is felt, however, that the more important procedures are:

1. Expert supervision.
2. Adequate personnel.
3. Infection control in nurses and mothers.
4. Carrier control in nurses and mothers.
5. Sterilization of formulas.
6. Rigid isolation of infected cases.
7. Hand technique.

Epidemic Diarrhea of the Newborn as a Hospital Problem

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The main consideration in the construction of a new nursery or the reconstruction of an old one is efficiency, which may be achieved through the most economical use of the space for the best care of the infants and for minimal effort on the attendants' parts. This latter must be calculated in total effort and so the reduction of the total labor implies reduction in the number of attendants. The arrangement of the devices to be employed in the infants' care is important to save unnecessary labor and to obtain the optimal division of that labor. That is, a nurse should have duties which only a nurse can perform and not be forced to perform many small chores which an untrained person can do as well, but which cannot be assigned to the unskilled because of the nursery layout. Freeing the nurse from menial tasks should be an objective in all nursery design, for the nearer this ideal is approached the higher the level of infant care.

Another important point in nursery design is the reduction of the number of people who must have access to the nursery. As far as possible, the nurses on duty should be the only ones to have access to this room. Attending physicians should enter for emergency purposes only and routine examinations should be conducted in an examining room to which the patient is brought. Before entering this room the physician should scrub thoroughly at the nurses' station after hanging his overcoat and hat and preferably his suit coat and vest on hooks provided outside the nursery station. Autoclaved mask, cap and gown are donned,

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and then the doctor may go into the examining room which is guarded by an ultraviolet light curtain as well as by doors. Incidentally, all the doors to this room should swing inward so that the opening of one forces the others to close. When he has completed his examination he returns to the outside before removing his gown, mask, and cap.

The examining room can be an alcove in an entrance anteroom. Its doors serve to block free air passage from the rest of the hospital to the nursery and are protected by light barriers. No other entrance need be provided. The second door can open directly into the nursery and a third opposite the second, directly into the utility room. All service facilities for the nursery are conducted from the outside corridor by means of the utility room, which will be discussed later.

The most desirable nursery is one which is cubicled with 7 ft. walls, largely of glass. In each cubicle is the equipment to be used for that infant. This includes a nurse's gown. In the nursery there is no desk, as the charting desk is in the nurses' station outside the entrance where the nurses can sit charting while watching the infants through a large glass panel. Opposite the cubicles is a small wash basin with foot controls, the only other article of equipment in this room. The temperature should be held between 70 and 75 degrees F. and the humidity between 30 and 50 R. H. In a nursery it is preferable to sterilize the air with a glycol vapor which renders the air bactericidal and permeates the entire nursery suite. The floor is of composition, either of the type which is laid in place or that which is poured like concrete. The ceiling is of sound-deadening material and is in soft color contrast with two-tone walls. In such a quiet nursery of soft colors and diffuse lighting, fatigue and nervous tension can be reduced.

Temperature, humidity, and ventilation must be regarded seriously for the health of the infants and the efficiency of the nurses. Wide differences of opinion exist on temperature and humidity. English nurseries, according to a survey in the *Lancet* (August, 1946), are considered too hot if they are above 60° F., while the tendency in the United States is to subject infants and nurses alike to 75° or more. It is common practice in this country to maintain the temperature of the newborn nursery around 85° F. This is true even when certain infants are kept in individually heated beds. These high temperatures have an enervating effect upon the nurses and are insufficiently high for the infants themselves. It is obviously more desirable to regulate the environmental conditions of these two groups independently of each other and means of accomplishing this will be discussed later. In nurseries where there are well, full-term infants only it is unnecessary to maintain uncomfortably high temperatures.

At this point it might be well to consider the complete elimination of the private newborn nursery, because this type of nursery is more open to the introduction of infections due to the larger number of individuals who have access to it. Any member of the obstetrical staff or pediatric staff may have private patients here and each infant may have his own private nurse. Ideally, each private newborn infant would be kept in a sound-dampened cubicle attached to his mother's room. This would insure complete segregation of all infants from each other and minimize the possibilities of cross-infection.

Since this ultimate ideal is not practicable in most hospitals, the second best choice seems to be a cubicled nursery such as described before, where each cubicle functions as an independent unit with bathing facilities and the individual supplies for each infant in his own cubicle.

Since it is nearly always necessary to compromise between the ideal and the practical, a utility room in which scrupulous technique is maintained should be considered for use in nurseries where no infections exist. This room should be adjacent to the nursery and separated from it by doors and ultraviolet light barriers. Into it, autoclaved linens are passed through a small window from the corridor to the linen shelf in the room. They are received, sorted, and stored in wall cabinets here. Along the same wall but separated by a glass partition soiled diapers are rinsed and dropped into a closed hamper which can be emptied from the corridor only. Against another wall stands a long infant wash table and scales.

These are separated from the clean linen shelves by a partial barrier of glass which is desirable only to prevent splashing. The linen inlet window should not be opened, of course, when an infant is in this section of the nursery. Along the wall at the end of the room lies a large sink with a left-side drainboard. Here the used formula bottles are cleaned and set into a sterilizer or pasteurizer to the right of the sink. This sterilizer extends through the wall under a large glass window into the sterile room of the formula preparation apartment, and it is in this sterile room that the sterilizer is controlled.

The formula preparation apartment is composed of two rooms. In the first is a door to the corridor and a window at table level, similar to that of the utility room's for admitting linens, cans, bottles, and other supplies. Dr. Weymuller believes that this receiving door should be a pasteurizer to prevent bacteria coming in on the supplies. Below it lies a small door for the removal of empty cans and the like to the corridor. Inside is a sink and cabinets for storage purposes. Separating this room from the sterile room, the first room beyond, is a swinging door guarded by an ultraviolet curtain. In the sterile room is the other end of the sterilizer mentioned above, the mixing table, a hot plate, a wash basin, and a telephone. There is no door to the nursery but large glass panels allow free view of it from two sides. Here the bottles, nipples and caps are received, sterile, from the utility room, and here the formulas are prepared. When each is bottled, and the nipple in place, it is capped with a metal or glass cap and returned to the sterilizer. After sterilization the formula is removed by the nursery nurse and stored in a refrigerator in the nursery.

Such a milk room arrangement could serve any type of nursery. The nurseries themselves, however, must be modified somewhat for specific purposes. Nurseries for private and ward newborn infants can follow much the described plan. Isolation nurseries, though, are usually set up along more rigid lines, by the isolating of sick infants in separate rooms with special nurses who do not attend other babies. In most hospitals this is the only solution to the problem of isolation. It is expensive in personnel, labor, and space. On this account the suggested alternative plan may be considered.

It is possible to separate infants completely in the same room by keeping them in separate sealed compartments. Air to each of these compartments is brought from out-of-doors where no pathogens exist, and is exhausted there separately. Feedings, linens, and other necessities reach the infant through a small airlock. This is a boxlike section with a door to the inside and one to the out, only one of which is opened at a time. The nurse reaches the child through sleeves on the front of the cabinet and can view him at all times through its glass windowed top. Batteries of such cubicles can be maintained at a common temperature and humidity by a single power-unit. In such a cubicle the infant is in out-of-doors air and is unexposed to air-borne bacteria. By being so enclosed he is guarded from droplet infection to which an attendant might expose him unwittingly. His exposure to contact infection is limited to the nurse's scrubbed hands. His protection against infection is greater in such a compartment than in a separate room, and the space and personnel advantages of such an arrangement are obvious.

Premature nurseries have all the requirements of isolation nurseries plus certain special ones of their own. Here the same careful isolation technique must be maintained, the infant must be protected from the same routes of infection (contact, droplet and air-borne). Additionally, each infant has definite and individual temperature and humidity requirements while these in isolation nurseries are the same for all. In general, the smaller the premature infant, the higher the environmental temperature required to maintain his body temperature at normal and the humidity in his environmental air affects his temperature requirements directly. For example, an infant of 2 to 2½ pounds may require 96° F. of dry air to keep his temperature at 98.6° F., while in humidities of 75 plus per cent R. H. he may have a normal body temperature in 90° F. air. Additionally, infants of 4 pounds and over suffer in the excessive humidities in which those smaller ones thrive, although most infants require supplemental heat until they reach 5 pounds. Thus the selection of the temperature and humidity for each infant must be done individually. Nurses in their masks, caps and gowns suffer even from the heat required by the larger of these infants. As this is the case, it

seems logical to allow the room to be at a temperature in which the nurse is comfortable and to have each infant in an incubator where the temperature and humidity can be optimal for him.

Incubators which depend upon convection currents for drawing in the air to the infant usually draw this air from near the floor. When these are in use, specially careful measures must be employed to minimize the number of bacteria in the air. Masks on the nurses and staff help to reduce the number of these bacteria, but as the air penetrates the mask, bacteria can be carried in it. The real use of the mask is to prevent the fall of droplets from the mouth and nose. One of its greatest disadvantages is in the discomfort it produces with the consequent inclination on the wearer's part to adjust it with the fingers. This changes the route of contamination to one of contact with the bacteria, but strict self-discipline can probably minimize this. However, it does seem safest to care for the infant in such an apparatus as was described for isolation rooms and which has, in addition, temperature and humidity control and regulation.

To conclude then, nursery design should consider all measures for the safety of the infant and the comfort and convenience of the nurse as means toward the same end.

CONCLUSION

DR. CLIFFORD.—The preceding discussion demonstrates that there is no justification for a fatalistic attitude concerning the problem of diarrhea in newborn infants.

Most of the outbreaks are the result of plain, common, ordinary "filth." It is shocking to hear of contaminated common thermometers, formulas, nipples, examining instruments, nursery basins, enema solutions, subcutaneous saline solutions, soap solutions, sterilizing solutions for hand dips, table tops, and hand brushes in modern newborn infant nurseries. It is shocking to hear of infants infected with organisms that can originate only in the human gastrointestinal tract.

The universal adoption and enforcement of the simple and practical "Standards and Recommendations for Hospital Care of Newborn Infants (Children's Bureau publication No. 292)" would go a long way toward protecting the newborn infant from the hazards of diarrheal disease. All investigators emphasize the cardinal importance of plenty of soap and water in the prevention of infection in the nursery.

It may be that the coagulase positive staphylococcus counts on infants' stools as suggested by Cummings may prove to be a useful check on nursery technique, allowing correction prior to the outbreak of infection.

Experience has demonstrated carrier-borne infection of such importance in the etiology of newborn diarrhea that routine stool and throat cultures of nursery personnel are recommended.

True epidemic diarrhea of virus etiology may strike a nursery in spite of all known precautions. In this connection the words of Dr. Dodd are reassuring, "I have never seen a serious epidemic develop in a nursery where the babies were carefully watched by pediatricians, even though the physical facilities, except for the presence of plenty of soap and water for hand washing, were poor."

We have a very useful procedure at the Boston Lying-in Hospital that has demonstrated its ability to put the fire out at the start before a serious spread has occurred. The setup consists of a separate isolation room available for every nursery, into which any infant may be instantly transferred by the nurse in charge, without a physician's permission, at the first loose stool or other sign of infection. We have mobile nursery equipment permitting the conversion of any empty room into a temporary nursery.

If one baby in the nursery develops a diarrhea, that baby is isolated.

If two babies from a given nursery develop diarrhea, both babies are isolated and the nursery is *quarantined.* No new baby is admitted to that nursery until it is emptied and cleaned. All new babies are admitted to the temporary nursery.

If three babies from a given nursery should develop diarrhea, we will consider an epidemic is in progress and take the necessary steps, including the notification of the board of health.

DISCUSSION

DR. JAUDON.—How is the virus infection transmitted from mother to child?

DR. DODD.—We do not know, but some work which I have already mentioned makes it seem possible that the child acquires infection during passage through the birth canal.

DR. J. E. GUNDY, RYE, N. Y.—What about the transmission of infections to the babies by visitors?

DR. CUMMINGS.—Visitors are a potential source of infection to the babies by virtue of the fact that they are in contact with the mothers. Unrestricted visiting is certainly dangerous to the maternal population and, in turn, therefore, to the infant population. It is my belief that visitors should be limited to both mothers and nursery. A good rule is to limit visitors to two grandmothers and the father. In nurseries where the babies are not completely segregated from the outside personnel, visitors should be prohibited.

DR. CLIFFORD.—Will the Chapple compromise be satisfactory in preventing infections in the nursery?

DR. CUMMINGS.—I am not personally in a position to make recommendations regarding the Chapple technique. I believe, however, that this technique is one of the ways of controlling nursery infection.

DR. R. M. KEMPTON, SAGINAW, MICH.—Should a potential case of diarrhea of the newborn be termed epidemic diarrhea?

DR. CUMMINGS.—A potential case of diarrhea of the newborn should be termed epidemic diarrhea of the newborn until an absolute diagnosis can be made. However, a potential case of diarrhea of the newborn in a nursery should, from the standpoint of the hospital administrator and the attending staff, be considered as a potential case of epidemic diarrhea of the newborn until proved otherwise.

DR. KEMPTON.—How many cases of the diarrhea constitute an epidemic?

DR. CUMMINGS.—One case of diarrhea in a nursery should raise the question of epidemic possibilities. Two or more cases of diarrhea should be considered as an epidemic until proved otherwise.

DR. J. C. MONTGOMERY, DETROIT.—How difficult is it to gavage in Chapple bed?

DR. CHAPPLE.—It is not difficult, as the infant's bed can be propped up on the catches inside, a funnel holder bracket is on the wall, and the infant himself is so easily handled.

DR. C. O. LORIO, BATON ROUGE, LA.—What amount of glycol is to be used?

DR. CHAPPLE.—Approximately one part in five million parts of air with propylene glycol—about $\frac{1}{10}$ of this with tri-ethylene.

DR. JAUDON.—Would it be feasible to admit newborn infants from the outside to Chapple bed?

DR. CHAPPLE.—We do.

DR. CLIFFORD.—How do you cut down the bacteria count in the air in the nursery?

DR. CHAPPLE.—Our nursery is in a hospital for sick children, so we use ultraviolet lights as barriers and in overhead fixtures, and we plan to evaporate propylene glycol in certain rooms.

DR. J. H. LYDAY, DENVER.—What is the effect on nurses from breathing vapors of chemicals?

DR. CHAPPLE.—None. Dr. Robertson's studies on toxicity *proved* this beyond a doubt. Animals were subjected to many thousandfold the concentration for many months without harm.

DR. GUNDY.—What effect have chemicals on viruses?

DR. CHAPPLE.—Dr. Robertson believes the glycols kill many viruses as readily as they kill bacteria in the air.

DR. R. E. GROSS, BOSTON.—Is it necessary to heat and humidify each isolating unit individually?

DR. CHAPPLE.—While they can be built in batteries, back currents of air require that each has its own air supply; therefore, separate heat and humidity are usually employed as well. For premature infants this is absolutely necessary but for older infants heat might not be required beyond that gained from the nursery itself.

DR. DODD.—Isn't a cooling system needed too? It would be in Cincinnati.

DR. CHAPPLE.—In the insulated chambers, a small infant generates about 8° degrees of heat. If the room temperature comes with 8° F. of that required by the infant, cooling will be necessary.

DR. CLIFFORD.—How long should each newly admitted premature be placed in the Chapple isolation unit before being admitted to the regular premature nursery?

DR. CHAPPLE.—We keep them in the units their entire stay in the premature nursery, sending them home after acclimatizing them to room conditions in the unit.

DR. BARBOUR, PEORIA, ILL.—Is there any way that the glycols may be used in the various water humidifiers?

DR. CHAPPLE.—A humidifier which generates heat will evaporate glycols.

DR. CLIFFORD.—Thirty cubic feet per baby is the ideal standard setup by the Children's Bureau in nurseries for the newborn. Would not the Chapple unit be a good compromise with the Children's Bureau standard?

DR. CHAPPLE.—While I cannot answer for the Children's Bureau it would seem that it might be, as the air in the isolation unit is more free of pathogens and the baby has more fresh air in this greater volume.

DR. CLIFFORD.—What method is used for getting the glycols out into the nursery?

DR. CHAPPLE.—There are evaporating devices on the market, but any heat source such as a hot plate will serve. The glycol should be dripped from a burette at the rate required.

DR. GUNDY.—How many cubic centimeters should be evaporated per cubic foot?

DR. CHAPPLE.—Approximately .01 c.c. of propylene glycol and .001 c.c. of triethylene continuously.

DR. CLIFFORD.—Will the vapor condense noticeably or harmfully on the draperies or furniture?

DR. CHAPPLE.—It does condense on windows and doorknobs quite readily but not on draperies or furniture.

DR. B. HOYER, CINCINNATI.—What are the advantages of curtain irradiation at the door over overhead irradiation?

DR. CHAPPLE.—For most applications, the overhead method is the one of choice. When curtain irradiation across a doorway is used, it is to prevent the free passage of bacteria into or out of the space so protected.

DR. R. G. ALEMAN, NEW ORLEANS.—What about the transmission of heat from the ultraviolet lights?

DR. CHAPPLE.—It is not greater than from other 30 and 60 watt bulbs and so under most conditions is negligible. It does, however, exert some favorable effect on the circulation of air past the light.

DR. DODD.—What about the problem of getting the breast-fed baby out to his mother and back to the nursery without becoming infected?

DR. CHAPPLE.—Ideally he probably should be in the room with his mother, but if he is not he should be wrapped in a sterile sheet and conveyed by a nurse in a sterile gown who is masked and has freshly scrubbed hands.

Round Table Discussion on Tumors, Benign and Malignant

CHAIRMAN: HAROLD W. DARGEON, M.D., NEW YORK, N. Y.

ASSOCIATES: PAUL E. STEINER, M.D., CHICAGO, ILL.
RALPH E. HERENDEEN, M.D., NEW YORK, N. Y.
PAUL C. BUCY, M.D., CHICAGO, ILL.
JOHN H. DALE, JR., M.D., NEW YORK, N. Y.
HAROLD L. TEMPLE, M.D., NEW YORK, N. Y.
STUART N. ROWE, M.D., PITTSBURGH, PA.

SECRETARIES: JOHN A. BIGLER, M.D., HIGHLAND PARK, ILL.
EMELIE M. PERKINS, M.D., RUTLAND, VERMONT

CHAIRMAN DARGEON.—The title of our Round Table discussion, which is "Tumors, Benign and Malignant," requires clarification. It is not our purpose to consider benign and malignant tumors as two different, although related, groups of diseases, some of which may be fatal and others nonfatal. They will be reviewed rather as one entity; that is, the neoplastic process, whose manifestations may be quite variable but whose essential nature is similar in whatever form it occurs. From the pathological, clinical, and public health standpoints this approach is justified.

1. From the pathological: The problem to the student of childhood neoplasms is not alone the histologic diagnosis of the tumor but the recognition of the possible future effects of the anatomical and physiological changes of the growing child upon that tumor. That the growth process produces alteration in the tumors of children is suggested by the changes observed in such neoplasms as melanoma and neurofibroma. These may be benign initially, yet as age advances a certain number will become malignant. It is possible to determine the structure of most tumors by histologic study and, therefore, in many cases to predict the eventual course of the disease. Not infrequently, however, although the identification of the tumor may be made accurately, the future course in the individual patient may only be surmised.

2. From the clinical standpoint: The clinical appraisal of any disease requires a careful determination of the prognosis. Some benign tumors may be fatal. The difference between a benign and malignant neoplasm from the prognostic standpoint is often an academic one. To the individual patient the importance of the disease is not its name nor its statistical significance but whether or not he will recover from it.

3. From the public health standpoint: Our terms should be considered from the viewpoint of the entire childhood cancer control program. This necessarily concerns itself with lay education. Although physicians know that some benign tumors are incompatible with life, the word benign may suggest to the layman a security which is relatively or even absolutely unjustified. The word malignant, however, indicates to many people a hopeless disease. Hence, on the one hand we observe children with advanced disease who have not had a tumor treated because it was always considered harmless and, on the other hand, we see fatal cases in whom no therapy was attempted because the outcome was considered hopeless from the very beginning. It is preferable to consider all neoplasms as actually or potentially malignant and to use the word cancer in its broad meaning to include all tumors.

Tumors are observed infrequently in practice or in general hospital services; nevertheless, the very high cancer death rate places it in a conspicuous position among the causes of childhood mortality. A particularly unfortunate situation occurs in the ages from 1 to 4 years. In this age group, malignant tumors which are known to be curable in some instances, retinoblastoma, Wilms' tumors, and some somatic sarcomas, to name but a few, seem to occur more often than at other ages. In addition, a number of benign tumors, e.g., hemangiomas, lymphangiomas, ganglioneuromas, and neurofibromas, which are potentially

fatal, are observed before the fifth year. This age group, the preschool group, is not as well supervised medically as is the infant in his first year, or the school child from 6 years of age onward. Therefore, in an age group in which cancers with a not universally unfavorable prognosis occur, the unrecognized disease progresses because of lack of examination.

As would be expected from a disease which affects so many different parts of the body, the symptoms are multiple and varied. Yet the objective and subjective signs of all these neoplasms may be briefly summarized as: first, the unusual child, and second, the atypical case.

The child who shows significant differences—physically or mentally—from his fellows may have cancer. The child whose history is that of a "changed" person in that his present disorder has produced noticeable deviation from his usual mental or physical state may have cancer. The child who has a disease which appears to be diagnosed accurately initally but nevertheless runs an atypical course particularly of a chronic nature or with periodic recurrence may have cancer. I believe the various diangostic signs which will be discussed this morning can be considered under the classifications, the unusual child or the atypical case.

The following outline indicates the essential facts which are pertinent to the diagnosis of any type of childhood cancer.

Diagnosis of Childhood Cancer

I. Sites affected—six main body areas
II. Varying ages of occurrence of different types of cancer
III. Suggestive clinical observations applicable to many types
IV. Special clinical features of individual type

This series of 1,770 cases includes those from Memorial Hospital. Several series have been added together in an effort to attain a closer approximation of the actual situation pertaining to topographical distribution than might be suggested by a single series.

TOPOGRAPHICAL DISTRIBUTION OF 1,770 CASES OF CHILDREN'S CANCER FROM SEVEN REPORTED SERIES

C.N.S.	*Bones*	*Eye*	*G.U.*	*Lymph.*	*P.Sar.*	*Pharynx*	*Skin*
370	365	235	230	204	144	36	31
Abd.	*G.I.*	*Gyn.*	*Liver*	*Misc.*	*Sal.*	*Lung*	*Pancreas*	*Lip*
19	21	25	13	18	7	5	3	2

The topographical distribution of 573 cases of childhood cancer observed at Memorial Hospital was as follows:

TOPOGRAPHICAL DISTRIBUTION OF 573 CASES OF CHILDHOOD CANCER, CHILDREN'S DEPARTMENT, 1917-1946

	C.N.S.	*Bones*	*Eye & Orbit*	*G. U.*	*Lymph.*	*P. Sar.*
	12	36	25	22	8	37
		79	15	17	33	41
		55	31	24	61	58
Total		174	71	63	104	131
	Pharnyx	*Skin*	*Gyn.*	*Misc.*	*Sal.*	*Lip.*
	9	4	1	0	0	0
	14	2	6	5	4	2
	4	1	4	0	2	0
Total	27	7	11	5	6	2

There are six main body areas in which cancers commonly occur during childhood. They are the central nervous system, bones, eye, kidney, blood and lymphoid system, and skin and supporting tissues. This is of no importance to the patient if his disease happens to be located elsewhere but it has several points of importance in the over-all consideration of cancer diagnosis.

1. In attempting to diagnose a neoplastic disease in a child, the common cancers of the adult, namely those of the mouth, stomach, intestine, prostate, breast, and female genitalia, do not usually enter into the problem.

2. The cancers of children, with the exception of those of the central nervous system and some lymphomas, are readily accessible to examination. Thus a diagnosis may be frequently made on physical examination alone.

3. This accessibility also increases the feasibility of therapy.

THE MORTALITY INCIDENCE FROM NEOPLASMS IN THE UNITED STATES BY FIVE-YEAR GROUPS BETWEEN 1939 AND 1943.

AGE GROUP	CANCER AND OTHER TUMORS	LEUCEMIA	HODGKIN'S DISEASE
Birth to 4 years	3,095	2,430	
5 to 9 years	1,982	1,168	
10 to 14 years	1,976	895	

These general findings are not limited to tumors alone, but, as is evident, may occur in other diseases, especially chronic diseases.

Diagnosis of Childhood Cancer

III. Suggestive clinical observations
1. Changes in growth of (a) entire body
(b) individual members
2. Changes in temperament, behavior, intelligence, disposition
3. Swelling (nontraumatic)
4. Undiagnosed disorder of short or long duration

HEMANGIOMAS

Diagnosis.—Hemangiomas present little difficulty in diagnosis if the lesions are cutaneous.

Most subcutaneous hemangiomas must be differentiated from a large group of somatic tumors, including lymphangiomas, fibromas, myxomas, myomas, lipomas, neuromas, and their malignant counterparts. Biopsy is frequently necessary to establish the diagnosis.

Visceral hemangiomas may produce hemorrhage into a viscus with resultant physical signs in some instances. Visceral hemangiomas seldom occur without associated cutaneous lesions. Occasionally, however, a visceral hemangioma, intracranial, intrathoracic, osseous, which may be of serious consequence, will be present, and no external evidence of the disease will be apparent.

Management.—The pediatrician must decide whether or not treatment should be instituted, when it should begin, and what type should be employed. The decision to defer therapy is frequently made because of the consideration that spontaneous regression occurs in many hemangiomas. It is not possible to generalize about these tumors, but I believe the risks of not treating such a tumor particularly in early infancy must be carefully calculated before any recommendation is made.

The method of treatment selected depends upon the case. Cauterization with CO_2 snow, injection of sclerosing solutions, operative intervention, and, at times, radon seeds are the most accepted methods. A decision to treat hemangiomas or any other neoplasm in children by irradiation should be reached only after the possible effects of this form of therapy have been evaluated.

LYMPHANGIOMA

The cystic variety of lymphangioma is readily recognized. The diffuse subcutaneous lesions may have the brawny consistency of an inflammatory mass or may resemble any of the soft somatic varieties of tumors described above.

Visceral lymphangiomas occur (the mesenteric cyst is an example) and must be differentiated from other masses known to occur in the body area affected.

Treatment is usually operative, but sclerosing solutions are used with some success at times.

NEVI

Diagnosis.—Nevi are not, as a rule, difficult to diagnose. They include the pigmented mole or neuro nevus, the hairy mole, and the melanoma. All may be the sites of malignant melanoma in adolescence or later in life.

Management.—They should be removed surgically in childhood under these conditions:

1. The nevus is a true "blue black" melanoma.
2. The nevus is growing with rapidity.
3. Its location subjects it to trauma.
4. While cosmetic reasons are not always important, they have a place in some of our decisions about children. We find that although boys and girls do not seriously object to the presence of surgical scars they do resent being called "pussy cat," "mouse," or "monkey" by their associates, because of the presence of a conspicuous nevus.

NEUROFIBROMATOSIS

Diagnosis.—This curious constitutional disorder is characterized by all or some of these findings: café au lait spots, subcutaneous, submucous, or visceral fibromas sometimes of great size, osseous changes, and cerebral defects. There is a marked familial incidence in this disorder. Some 12 to 15 per cent of the tumors become malignant.

Treatment.—Surgical excision of any mass occurring in a child who has café au lait spots or a family history of neurofibromatosis.

RETINOBLASTOMA

This is one of the two highly malignant curable tumors observed with comparative frequency during early infancy. (The other is the Wilms' tumor of the kidney.) It seldom occurs after 5 years of age. Of forty-three cases at Memorial Hospital it was bilateral in twenty-eight (60 per cent). It arises from the granular layer of the retina, grows slowly in most instances, and produces few symptoms.

It is discovered usually by the parent who notices the peculiar "cat's eye" pupillary reflex in the affected eye. Other symptoms we have observed are: orbital bulge; conjunctival discharge and congestion; a squint; variation in the color of the pupillary reflex of gray, green, white, red, or yellow; disturbances directly related to impaired vision, crying when the unaffected eye is covered, stumbling, "clumsiness" and turning of the head to permit unaffected eye to be used.

There is usually a considerable delay before the child is treated. Of thirty-two cases in this series in which the history could be obtained, only eight were treated less than one month from onset, and six from one to three months. In eighteen children the delay was between three months and two years.

The diagnosis is made on the opthalmoscopic findings of a gray-white mass, vascular at times, sometimes containing calcium, flecks of which appear in the vitreous in some instances. Pseudogliomas, retrolental fibroplasia, congenital glaucoma, and tunica vasculosa lentis must be considered in the differential diagnosis.

If uncontrolled, metastases to bones, lymph nodes, subcutaneous areas, and viscera may occur.

The treatment is enucleation of the affected eye in unilateral cases. If tumors are found in both eyes, the more seriously affected eye is enucleated. Removal of the other eye may be considered, but under the method of high voltage radiation, as outlined by Martin and Reese, the preservation of sight and destruction of the tumor may be expected in some of these cases.

The familial incidence of this tumor has been known for some years. This was also the case in two families in this series.

NEUROBLASTOMA

This tumor may occur at any age in childhood but its greatest frequency in our experience is during the first five years of life.

It arises from the sympathetic neuroblast and the primary lesion may occur in various localities. The adrenal medulla is probably the most common primary site. It may also occur in the celiac plexus, the cervical, thoracic, sympathetic and intracranial as well as in the peripheral nerves.

The course is moderate to extensive local spread and metastases to liver, lymph nodes, and bones; particularly the skull. It is an embryonal type of tumor and may mature into a benign ganglioneuroma in rare instances. It may also develop into a chromaffinoma, a tumor associated with considerable vasomotor disturbances.

An early diagnosis is difficult and is finally made only on biopsy. Its presence must be suspected in the diagnosis of abdominal and intrathoracic masses as well as by lymphadenopathy. Unfortunately the earliest indications of this cancer in many cases are the skull metastases, which appear about the orbital and auricular areas as well as the skull vault.

Treatment is by removal, when possible, and otherwise by irradiation.

LYMPHOID STRUCTURES AND BLOOD-FORMING ORGANS

The diagnosis of leucemia requires no discussion in this group. The diagnosis of Hodgkin's disease and lymphosarcoma may be made positively only by aspiration or formal biopsy.

Inasmuch as these cancers may affect a great variety of tissues, their clinical evidences may be few or many as well as quite varied.

Management.—A lymphosarcoma, if localized, should be excised if its situation makes this feasible. Hodgkin's disease and inoperable lymphosarcomas are treated with irradiation.

The leucemias in children are not irradiated. We have used urethane (ethyl carbamate) in three cases of myeloid leucemia in children.

The nitrogen mustards (HN_2: Di-beta-chlorethylamine and HN_3 Tri-beta-chlorethylamine) in use up to 1946 were not effective in leucemia. Another compound of this group has been used on three children (see accompanying tables) and the decline in the total white counts has been constant enough to recommend further study. It appears that this compound has some palliative effect, the extent of which cannot be appraised at this time.

WILMS' TUMOR

Diagnosis.—The subjective symptoms of this tumor do not begin until the disease has progressed. The earliest diagnostic sign is usually that of an abdominal mass in the upper quadrant or in the flank.

It is to be differentiated from other intra-abdominal and renal tumors, splenomegalies, hepatomegalies and some inflammatory processes, notably tuberculous peritonitis.

The intravenous and retrograde pyelogram show alterations in size, position, and configuration of the kidney, pelvis and calyces.

A positive diagnosis may be made only at operation, although a presumptive diagnosis is possible in almost all cases by clinical findings. A biopsy should never be performed inasmuch as the tumor is usually well localized (some believe encapsulated) in the kidney and biopsy may produce spread regionally and systemically.

Management.—Surgical removal is recommended as early as possible. Irradiation preoperatively is advocated by some surgeons, particularly if the mass is extremely large. Postoperative irradiation has been advocated by many. I feel that the problem of the individual case must determine the course to pursue.

CONCLUDING REMARKS

It is evident that we are faced with a formidable task in our efforts to reduce the number of deaths among children from neoplasms.

While we must await further discoveries in the research fields before cancer will be completely conquered, there are some simple and obvious policies which, if now adopted, would be of immediate benefit.

From the layman's standpoint: (1) The public must know that these diseases constitute a very real hazard during childhood. (2) The great importance of continuing the periodic medical examination of the child which this and other medical societies have long

S. K., FEMALE, AGED 4 YEARS. BORN 2/19/43. ADM. NOV. 8, 1946. WEIGHT 39 LB.

	BLOOD FINDINGS						
	10/23/46	10/24/46	10/28/46	11/11/46	11/29/46	12/23/46	1/17/47
WBC	450,000	450,000	434,000	360,000	80,000	3.8	13.2
M. Blast.	1						
Mcytes.	33	36	40		51		2
Meta.	10	8	8				2
Nonseg.	30	30	42				7
Seg.	30	30	8				56
L-cytes			1.5		1		26
Prothr.	100%						
Plate.	145						
Hgb.		8.5		7.7	3.4	10.2	11.6
RBC							4.3
Eosin.		1			3		2.0
	URETH.	*Dose* .9		*Dose* 1.8	*Dose* 2.0		

Sternal Marrow

Total Nucl.	566,000
Megak.	11
M. Blast.	1.0
Myelocyt.	41.5
Meta.	7.5
Nonseg.	35.5
Seg.	11.5
Lymph.	0.5
Nu. RBC	2.5
Peroxidase pos.	93.0%

J. P., MALE, 4 MONTHS OLD. BORN 5/4/46. ADMITTED 10/7/46. WEIGHT 14 LB.

	BLOOD FINDINGS				
	1/25/46	11/11/46	12/12/46	1/17/46	2/7/46
WBC	56,200	20,5	13,2	16,7	34,
M. Blast.	2%				
Mcytes.	16.5	4	1		7
Meta.		7	17	2	
Nonseg.	16	36	17	5	2
Seg.	19		30	11	29
Lympho.	46.5	43	43	40	50
Prothr.	100%				
Platel.	80,000				
RBC					
Hgb.	14.8	15.1	12.3	10.2	8.3
Eosin.				16	11
Nuc. RBC	1				
	Dose	*Dose*	Disct.		
URETH.	0.25	2 c.c.			

Sternal Marrow
(10/25/46)

Total Nucl.	297,500
Megak.	0
Myelobl.	1.0
Myelocytes	48
Nonsegs.	41
Segs.	2
Lymphocytes	1.5
Nucl. RBC	6.5
Peroxidase positive	88%

E. N., FEMALE, AGED 10 YEARS. BORN 3/19/36. ADM. 8/22/46. WEIGHT ?

BLOOD FINDINGS

	8/22/46	8/28/46	8/30/46	9/16/46
WBC	30.0	15.0	12.4	8.6
Blasts unidentified	35			
Baso.		14	47	
Mono.		51	51	
Lymph.	65	1	1	
Segs.			1	
Nonsegs.				
Hgb.	13.7	10.2	11.6	73%
RBC.	Mod. ach.	3.8		

	Dose
URETH.	1 gm. t.i.d.

Sternal Marrow

P	1
Stab.	2
Ly.	22
Early blasts	59
Metas.	3
Blast.	13
Nr	2% (late)

advocated not only during but following infancy cannot be overemphasized. (3) Cancer should be made a reportable disease. Our mortality statistics are relatively satisfactory but the morbidity rates, certainly among children, are not.

From the physician's standpoint: (1) A revision in our approach to the differential diagnosis of swellings, obscure symptoms, and physical and psychological peculiarities would seem indicated by the study of the histories in a comparatively large series of children's cancers. Neoplasms must occupy a primary position in the consideration of any of these conditions, not because of frequency but because of the risk involved if the disease is overlooked. (2) The necessity of a prompt and thorough investigation of any suspicious masses or symptom complex is evident. (3) The early and more general use of the aspiration biopsy is advocated. (4) We must appreciate that there is no such thing an as early diagnosis of childhood cancer. Although we may be able to diagnose the disease soon after the onset of symptoms, the life of the tumor may antedate a diagnosis by months or years.

The collaboration of the parent, physician, surgeon, pathologist, roentgenologist, radiologist, and health officer is necessary in each case of childhood cancer if unnecessary deaths from this group of diseases are to be prevented.

The Radiological Aspects of Benign and Malignant Tumors in Infants and Children

John H. Dale, Jr., M.D., New York

In a general pediatric service, the incidence of benign and malignant tumors in infancy and childhood, excluding hemangiomas and the lymphoblastoma group, is low in proportion to other conditions. Conversely, the mortality rate of the malignant group and of some of the benign group equals or surpasses that of the more common diseases. This has been true in our experience at the Children's Clinic of The New York Hospital during the past fifteen years.

It has been our experience that the radiologist is seldom called upon to examine those patients in whom the tumors are so located that the diagnosis is readily afforded, either through a physical examination or through tissue study subsequent to biopsy of the tumor. Consequently, our records reveal few examples of the somatic soft tissue tumors, such as lipomas, neurofibromas, neurosarcomas, and cutaneous hemangiomas.

Excluding tumors of the central nervous system, the most common locations of the benign and malignant tumors, from the radiological point of view, have been the skeletal system, the kidney and the adrenal glands, and the mediastinum.

In the skeletal system, the most frequent benign tumors have been those classified as the benign osteogenic tumors. These arise from bone and/or cartilage, and include the osteomas and the osteochondromas or exostoses.

The osteoma arises from the unbroken cortex of the bone and appears radiologically as a rather well-circumscribed outgrowth of bone. This tumor is usually found between the ages of 8 and 19 years. It grows slowly and does not become malignant. The flat type is the most frequently described form.

The osteochondroma arises from the shaft of the bone in the vicinity of the attachment of tendons, hence the most common location is at the end of the shaft near the joint. Two forms are usually seen: the flat and the pedunculated. In both, the bony base is covered with a cartilaginous cap which imparts the irregular outline and the radiolucent areas seen on the x-ray film. Both arise from the unbroken cortex and the shaft is generally thickened at the site of the tumor. The direction of growth of the pedunculated type is that of the greatest muscular pull. There is often a clear demarcation between the bony base and the cartilaginous cap. Both forms may undergo malignant degeneration and give rise to secondary chondrosarcomas which are highly malignant and resistant to irradiation therapy. This change is rare in childhood and usually occurs after puberty.

In searching the files for examples of the nonosteogenic type of tumor in the age group represented in the Children's Clinic, I was unable to find any cases of the more common bone cysts and benign giant cell tumors. The examples of these lesions are taken from the pediatric service of the Memorial Hospital, which maintains an active tumor service.

Bone cysts are localized, fibrocystic, destructive lesions with no power of bone formation. They are almost always found under the age of 15 years. The most frequent sites are in the metaphyses of the proximal ends of the femurs, tibias, and the humeri. Radiologically, they appear as well-defined, radiolucent areas. The medullary cavity is dilated, and the cortex is eroded and thinned from the inside. The normal bone markings in the area of the lesion are destroyed and the cyst may present a multilocular appearance. In contrast to the giant cell tumors, the bone cyst is limited to the shaft side of the epiphyseal line and does not involve the epiphysis. The cortex is intact but is sometimes ruptured if the tumor grows to an excessive size. Pathological fractures occur at the site of the cysts and lead to a reparative periosteal reaction. Enchondromas are identical in their radiological appearance but they are usually limited to the small bones of the hands and feet or to the vertebral bodies or sternum. Myelomas are found in the same locations as cysts, but they are vaguely outlined and destroy the cortex without expanding the medullary cavity. This type of tumor is rare in childhood. Solitary abscesses may be confused with bone cysts. The former are almost always found in the proximal end of the tibia.

The giant cell tumor of bone resembles the bone cyst and is found in the same anatomical sites as well as in the distal ends of the radii and femurs. It has been stated by Geschickter that 90 per cent of the tumors of the distol end of the radius are giant cell tumors. The tumor is rare in childhood. As the slide illustrates, the main point of differentiation from the bone cyst lies in the fact that the giant cell tumor is not limited to the shaft side of the epiphyseal line and tends to involve the epiphysis as well as the spongiosa of the metaphysis. The medullary cavity is expanded and the cortex is thinned and ruptured from the inside as in the bone cyst. Since the tumor has no power of bone formation, no new bone is seen except the reparative periosteal reaction, which follows pathologic fracture through the site of the lesion. A small percentage of giant cell tumors undergo malignant change. In contrast to bone cysts, the giant cell tumor does respond to irradiation therapy.

Bucy and Capp, in 1930, reported on primary hemangiomas of bone. They described the radiological findings of the lesion in the tubular and the flat bone. We have seen very few involving either type of bone. The intraosseous hemangioma of tubular bone is well demonstrated in the next slide. The involved metacarpal bone shows a central, expansive type of lesion with a peculiar multioculated or soap-bubble appearance. The cortex is thinned and the medullary cavity is dilated. There is no periosteal reaction, such as has been

described by Sherman in a similar tumor of the femur of a 2½-year-old girl. The soft tissues of the third finger are hypertrophied and clinically this finger was involved by a cavernous type of hemangioma.

In the vertebrae, the hemangiomas are recognized radiologically by the thickening of the vertical trabeculae. These lesions are said to occur in about 11 per cent of autopsies and often remain silent during the life of the individual.

In the flat bones, the picture is different and characteristic. Here one sees a sunburst radiation of trabecular markings radiating from a common center. The periosteum remains intact but may be elevated.

Malignant osteogenic tumors of the bone are rare in infants and children. In the past fifteen years we have had 16,800 admissions under the age of 13 years, and we have not had a case of osteogenic sarcoma.

The osteogenic tumors are most common during puberty. They usually occur in the long bones near the epiphyseal line. They are rare in the center of the shaft. The osteoblastic type occurs most frequently in the humerus, femur, and the tibia about the age of puberty. The early radiological signs are an increased density or sclerosis of the medullary cavity and a periosteal thickening. After the tumor has broken through the periosteum and invaded the soft tissue, the characteristic sun-ray radiation of spicules perpendicular to the shaft of the bone are seen. These radiate into the soft tissue tumor mass. There is little visualized destruction of the bone, as can be seen on the slide. The radiation is well demonstrated, as is the increased density and the small amount of cortical destruction.

The osteolytic type causes no widening of the shaft as was seen in the osteoblastic type and no new bone formation in the form of spicules is seen. There is marked destruction of the medullary cavity and the cortex. As a rule, this type rapidly destroys the bone and invades the soft tissue early in the course. Both types of osteogenic sarcoma metastasize to the lungs and both are radioresistant.

The only nonosteogenic malignant tumor of childhood is the Ewing's endothelioma. We have had two cases in fifteen years. One was of the rib and the second of the ilium. Ewing's tumor may arise from the tubular or from the flat bones. The tumor metastasizes early, mainly to the lungs, and is very malignant. It responds well to irradiation at first, and then seems to become resistant. The initial response to irradiation may so change the cellular composition of the tumor that it becomes impossible for the pathologist to make a diagnosis. The use of the response to irradiation as a means of differential diagnosis should be evaluated with this fact in mind.

In the long bones the tumor is first seen radiologically as a thickening of the cortex and a widening of the medullary cavity, followed by a splitting or lamination of the periosteum to give an onion-skin appearance. At this stage, the radiological picture is often mistaken for osteomyelitis and it is here that biopsy is of the greatest value in establishing the true diagnosis. As the tumor progresses, there is extensive destruction of the spongiosa and the cortex, sun-ray radiation of spicules into the soft tissue mass may appear, similar to the osteoblastic type of osteogenic sarcoma, and there may be involvement of the epiphysis. Although the usual site is at the end of the long bones, the tumor may arise anywhere along the shaft and eventually involves over a third of the bone.

In the rib, as this slide demonstrates, extensive destruction is seen with the appearance of many areas of radiolucency. The mottled appearance is said to be frequently seen and often there is direct extension to the pleura with the formation of a bloody pleural exudate as is suggested in this case.

When Ewing's endothelioma arises in a flat bone, the radiological picture changes markedly. In this case, the ilium is involved. It has the appearance of increased density and sclerosis of the bone without destruction of the cortex. Close inspection of the film reveals the area to have a mottled appearance. This was called osteomyelitis until a biopsy was done and the diagnosis established. The response to irradiation was good and the bone returned toward normal, only to present a recurrence later with the development of pulmonary metastases and death in about a year.

Secondary or metastatic tumors of bone are seen with the lymphoblastoma group of tumors, with neuroblastomas of the adrenal glands, with retroperitoneal sarcomas, and very

rarely with Wilm's tumors of the kidney. The characteristics of these will be pointed out in the discussion of the primary tumors.

Excluding the lymphoblastoma group and the central nervous system tumors, the commonest malignant tumor of infants and children has been the Wilm's mixed embryonal or adenomyofibrosarcoma. Eight such patients have been diagnosed in the past fifteen years. Seven are dead and one is alive seven months after operation. Six of the eight cases occurred under the age of 5 years and, of these, five were in children under 3 years of age. The radiological examination revealed a large mass in the region of the kidney, with displacement of the renal pelvis and calyceal system of the involved side on retrograde pyelography. On intravenous pyelography, there was a failure to visualize the upper urinary tract in all of the cases in which this method was used. The same radiological picture is often seen with neuroblastomas of the adrenal gland and with retroperitoneal sarcomas. In neuroblastomas, we have found calcification in the tumor in over half of the cases. This has been reported by Bachman, Parsons, and Blatt as characteristic of this type of tumor. Neuroblastomas metastasize to bone relatively early, while Wilm's tumors rarely involve bone but tend to metastasize to the lungs. The retroperitoneal sarcomas tend to spread to the bone and into the abdominal cavity. The Wilm's tumors present a solitary or multiple nodular involvement of the lung, tending to concentrate in the lower lung fields. The multiple nodules are circular, well defined, and tend to be of the same size. This is not diagnostic, since Ewing's sarcoma and osteogenic sarcoma present the same picture, but, in the light of a tumor in the region of the kidney, the appearance of the lung metastases takes on more importance.

The next slides illustrate the commonly found tumor mass and two of the variations of the renal pelvis displacement and distortion seen as a result of the tumor growth. The degree of displacement and distortion depends upon the location of the tumor in the kidney.

The variations of the pulmonary metastases are well demonstrated in the following group of slides. The first is one of a solitary large nodule. It appears to occupy most of the right upper lobe. Clinically, it did not cause bronchial obstruction. The lack of obstructive symptoms is common in children, while in adults, obstructive signs and symptoms are often the first warnings of pulmonary metastatic involvement.

Multiple metastases tend to be discrete, of the same size, and tend to concentrate in the lower lung fields. The radiological picture, as I have stated, is not diagnostic but is very suggestive, especially with the knowledge of a mass in the kidney area or of an operation in this region.

The largest group of malignant conditions we have encountered has been the lymphoblastomas. Leucemia and Hodgkin's disease have occurred most frequently. These cannot be differentiated radiologically when they involve the mediastinal lymph nodes. In our experience, Hodgkin's disease has been the commoner in this location. The sternal marrow, peripheral blood studies, and biopsy of the superficial lymph nodes establish the diagnosis. The radiological examination merely adds confirmatory evidence. Both of the conditions may involve the mediastinal nodes and present similar pictures. Both respond well to irradiation.

The following illustrate the advanced state of Hodgkin's disease and the good response following radiation. The earlier state of the disease in the mediastinum shows the bilateral enlargement of the hilar nodes and the increased bronchovascular markings.

The acute lymphatic leucemia of childhood often shows changes in the bone on x-ray. As pointed out by Baty and Vogt, one constant finding has been the band of radiolucency proximal to the metaphysis, usually at the distal end of the femur. It may be found at the distal end of the tibia. In our series of over sixty cases, this has been a common finding. This is not pathognomonic and is found in many conditions which lead to a poor nutrition of bone. In the more advanced stages of marrow involvement and replacement, actual destruction of the bone may be seen, as illustrated in the following. Here one can see the areas of radiolucency in the metacarpals and phalanges, the osteoporosis, and the destruction of the cortex. Such a picture is seen in the neuroblastomas metastasizing from the adrenals. It is said that these metastases have a predilection for the proximal ends of the long bones, while leucemia usually is found at the distal ends. The neuroblastoma lesions have a peculiar quill-like radiation due to periosteal reaction. This is thought by Rypins to be seen most commonly in neuroblastoma. The lesions of the bone are widespread and the radiation is

perpendicular to the shaft of the bone. Leucemia very seldom shows periosteal reaction, and the lesions are not widespread as a rule.

Leucemia may sometimes invade the diploic spaces of the skull and give rise to a mottled appearance with bone destruction. The same may be seen with neuroblastoma and with lymphosarcoma.

Mediastinal tumors, other than the lymphoblastomas discussed previously, have been rare in our experience. We have seen one ganglioneuroma located in the usual position for such tumors, the posterior mediastinum. It caused its symptoms purely through pressure. The final diagnosis was made at the operation. One thymoma of the small cell sarcoma type was encountered. This was also proved at operation. The radiological pictures of these two lesions are illustrated in these last two slides.

Very occasionally we have diagnosed polypi of the large intestine by means of the barium enema and air contrast studies. Polypi have been rare in our patients. Occasionally they may become malignant, hence their recognition and removal are important. The combination of barium and air contrast studies is a helpful means of demonstrating the sessile and the pedunculated tumors of this nature, as the slide reveals.

The radiological examination is not infallible in the diagnosis of tumors of the various systems of the body, but it is of the greatest aid in the early recognition or exclusion of many of the conditions. In others it merely adds to the completeness of more obvious conditions. It should be used as much as possible and the examinations repeated if the first does not reveal the evidences of the pathology suspected. The radiological examination must be combined with the information gained by the other methods of investigation in order to be of the maximum value. In the early stages of bone tumors, the radiological changes are so slight that they may be overlooked unless the radiologist has had a wide experience in such conditions. The results of the roentgen examination should be checked by biopsy whenever possible to diagnose definitely the early tumors, since only the early recognition and treatment give hope for survival.

Tumors of the Brain in Childhood

Paul C. Bucy, M.D.,* Chicago

I. Metastatic tumors
II. Infratentorial tumors
    A. Tumors of the brain stem
    B. Malignant tumors of the cerebellum
        i. Medulloblastomas
        ii. Sarcomas of the meninges
    C. Ependymomas of the fourth ventricle
    D. Astrocytomas of the cerebellum
III. Supratentorial tumors
    A. Pineal tumors
    B. Tumors of the hypothalamus and optic chiasm
    C. Craniopharyngiomas

Unlike tumors elsewhere in the body, tumors of the brain do not readily lend themselves to subdivision into malignant and benign types which classification is so useful with tumors in other parts of the body. Tumors of the brain present quite a different problem. In many instances they are as "malignant" as tumors elsewhere, in that they cause the death of the patient. Likewise, they invade and destroy normal tissue. But, except for those occasional tumors which have spread to the brain from other parts of the body, they do not metastasize outside of the central nervous system. It becomes necessary, therefore, to classify tumors of the brain upon a different basis. The two most important differential criteria are the growth characteristics and the sites of predilection of the different tumors.

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METASTATIC TUMORS

Metastatic tumors of the brain are rare in childhood. One of the better known is the retinoblastoma of the eye which spreads to the brain as well as to other parts of the body. However, any tumor of this type is so uncommon as to merit little attention here.

Primary tumors of the brain fall naturally into two large groups. Those which appear above the tentorium cerebelli and those which develop in the cerebellar fossa. Unlike adults, children suffer frequently from tumors below the tentorium. In fact, over two-thirds of all of the tumors which occur during childhood are found in that location.

INFRATENTORIAL TUMORS

Infratentorial tumors found in children fall into four definite groups. They are the tumors of the brain stem, the malignant tumors of the posterior midline of the cerebellum, astrocytomas of the cerebellum, and the ependymomas of the fourth ventricle.

Tumors of the Brain Stem differ in one striking way from all other common intracranial tumors in childhood; they are seldom associated with increased intracranial tension. These tumors usually arise in the pons, although occasionally the medulla oblongata or the midbrain is primarily involved. The most characteristic symptoms are the paralysis of one or more cranial nerves. The sixth or abducens nerves are most frequently affected, with a resulting paralysis of lateral movement of the eyes. However, the destruction of the facial nerve and of the motor nucleus of the fifth cranial nerve with paralysis of the muscles of the face and of mastication is not uncommon. Frequently, the ninth and tenth nerves are involved, so that the child has difficulty swallowing and talking. Sensation may occasionally be lost in the face on one side, and even more uncommonly on the opposite side of the body. Although the long fiber tracts which are concerned with sensation are not often sufficiently involved to give rise to much that is obvious on examination, the motor and cerebellar pathways are usually affected. The result is varying degrees of paralysis, disturbances of reflexes, and severe incoordination with disturbances of voluntary control of the movements of the extremities, and a marked uncertainty of station and gait. Frequently, these children suffer from severe nausea and vomiting. This difficulty plus the trouble in swallowing which affects so many of them often results in a severe loss in weight with an early emaciation.

Because the signs of increased intracranial pressure are rarely found in these children they are often misdiagnosed as suffering from an encephalitis. This error is further contributed to by the fact that these children frequently run a low-grade fever, and it is not uncommon to find a moderate increase in white cells in the spinal fluid. However, the differential diagnosis is usually made simple by a slowly progressive development which extends over a much longer period of time than one would expect of an encephalitis.

Unfortunately, there is no satisfactory treatment for tumors of this type. Most of them progress rather rapidly, although in a few instances the condition may extend over a period of years.

All of the other tumors in the posterior fossa are characterized by the signs and symptoms of increased intracranial pressure. Of these, vomiting is one of the earliest. Although projectile vomiting may occur, the vomiting may differ in no regard from that seen with gastrointestinal disturbances. It commonly occurs in the early morning shortly after arising, and even before the child has eaten. But it may occur at other times. Headache, likewise, is commonly of the early morning variety. The location of the pain is usually of little localizing significance. And in many children the discomfort of the headaches does not seem proportionate to the other symptoms. Children's heads, unlike those of adults, can expand in response to intracranial hypertension. As a result, the heads become too large for the children's caps, and on x-ray examination of the skull the sutures will be found to be widened and the bones of the skull separated. This fact is said to give rise to a peculiar note on percussion of the skull, known as Macewen's sign. This sign, however, is not a reliable one. Increased intracranial pressure also gives rise to choking of the optic discs or papilloedema. However, as such edema of the optic nerve head does not result in any

disturbance of vision until late in its course, when secondary optic atrophy has occurred, it is found only on careful and complete examination. Paralysis of one or both abducens nerves with a resulting crossing of the eyes and double vision is a not uncommon result of increased intracranical pressure and a cause of serious disturbance of the child's vision.

These symptoms of intracranial hypertension may occur with any of the intracranial tumors, or with any other condition which increases the intracranial pressure. They are, therefore, of little help in determining the nature or location of the tumor. However, each one of the tumors has clinical characteristics of its own which makes it possible to recognize the kind as well as the location of the tumor in most cases.

Malignant Tumor of the Cerebellum are common tumors in children. Pathologically they fall into two groups, the medulloblastomas and the sarcomas of the meninges. The *medulloblastomas* occur predominantly in boys, usually about 5 years of age. Because the posterior part of the midline of the cerebellum where they develop is part of the vestibular mechanism and is concerned with the maintenance of balance, these tumors are characterized by unsteadiness of posture and of gait. There may be little else in the way of symptomatology apart from the signs of increased intracranial pressure noted above. These are rapidly growing tumors. They tend to spread through the pathways of the cerebrospinal fluid to produce implants of tumor on the surface of the remainder of the brain and spinal cord. No tumor of this type has ever been successfully removed. They are very susceptible to x-rays. Unfortunately, this susceptibility does not persist and in the course of one to three years the tumor again begins to grow despite enormous doses of radiation and soon results in the death of the child.

Sarcomas of the meninges do not present such a uniform picture as do the medulloblastomas. They are most common in the posterior fossa, but may occur in the cerebrum. They may arise in the posterior midline of the cerebellum, just as the medulloblastomas do, but are also frequently found on the superior surface of one of the cerebellar hemispheres. They may occur in young boys, but they are as frequent in girls as in boys and may occur in young adults as well as in children. When they occur in the midline of the posterior part of the cerebellum of young children they do not vary greatly in their course from the situation just described with medulloblastomas. That is, they respond to the x-rays for a time, but soon run a rapidly fatal course. However, when they occur in adolescents or in young adults the outlook is often much more favorable, and with extirpation and intensive x-ray therapy some of these people have lived for many years in relatively good health.

Ependymomas of the Fourth Ventricle are often indistinguishable clinically from a medulloblastoma. Although they grow more slowly than do the medulloblastomas or the meningeal sarcomas and do not appear as malignant microscopically as do these other tumors, the outlook is just as unfavorable in most instances. As they lie in the fourth ventricle and compress the brainstem to a thin layer, and also as they arise from the floor of the ventricle and invade the vital tissues in that region, their complete removal is almost impossible. The mortality of operations upon this type of tumor is very high. They are not favorably influenced by x-rays.

Astrocytomas of the Cerebellum are fortunately the most common single type of tumor which occurs within the intracranial cavity in children. They usually arise in or near the vermis but grow laterally to involve one of the cerebellar hemispheres. Furthermore, they usually are associated with a cyst which lies within one of the cerebellar hemispheres. Because of this lateralized character of these tumors they typically produce symptoms of cerebellar dysfunction which predominantly involve the extremities on one side. These extremities are awkward or ataxic. The incoordination of the arm makes it difficult to eat and to write while the involvement of the leg causes the child to stagger and deviate toward the side of the tumor. There is usually a nystagmus of the eyes which is coarser on looking toward the side of the tumor and more rapid and fine on looking toward the other side. The extremities on the affected side are often hypotonic and the tendon reflexes may be diminished. The child's head is often tipped toward the side of the tumor. There are also the usual signs of increased intracranial tension which differ from those seen with the medulloblastoma and sarcoma only in that they usually develop somewhat more slowly.

These are among the most favorable of all tumors of the brain. They can usually be removed completely. When this can be accomplished the child usually makes a complete recovery and has no further trouble from this source. If such favorable results are to be accomplished a complete removal is essential. Evacuation of the cyst or removal of part of the tumor will not suffice. These tumors are not influenced by the x-rays.

SUPRATENTORIAL TUMORS

Tumors which occur above the the tentorium, like those in the posterior fossa, differ widely from the tumors which occur in adults. The vast majority of tumors occurring in adults arise in the cerebral hemispheres. That is a very uncommon location for a tumor in a child, and when one does occur there it is usually a sarcoma of the meninges. Most of the tumors occurring above the tentorium lie in or near the third ventricle. Three different types form the great majority of these. They are the pineal tumors, the tumors of the hypothalamus and optic chiasm, and the craniopharyngiomas.

Pineal Tumors, in addition to producing the symptoms of increased intracranial pressure, give rise also to symptoms of involvement of the midbrain. The most common of these symptoms is the paralysis of conjugate upward movement of the eyes. The pupillary light reflexes may also be lost; tremor and ataxia may develop because of involvement of the superior cerebellar peduncles and the red nuclei; and there may be evidence of compression of the motor pathways in the cerebral peduncles. Many of these tumors can only be correctly localized by ventriculography. They are extremely difficult to treat surgically. For that reason it is now rather generally thought best not to attempt to remove the tumor initially. Instead, the internal hydrocephalus is first relieved either by leaving a flanged needle in place in the lateral ventricle to provide continuous drainage or a third ventriculostomy is made in order to short-circuit the obstruction of the aqueduct. Then the patient is given x-ray therapy. Many respond surprisingly well to this treatment. Should it fail, a direct surgical attack upon the tumor can be considered. However, very few such attempts to remove the tumor have ended successfully.

Tumors of the Hypothalamus and Optic Chiasm may involve either one of these two structures predominantly. But in most instances both are involved but to varying degrees. Tumors of the optic chiasm occur typically in individuals who are victims of von Recklinghausen's neurofibromatosis. In many instances the peripheral manifestations of this disease, which is usually hereditary, are not striking. There may be only a café au lait patch on the skin, a few subcutaneous nodules, or a tumor along one of the peripheral nerves. However, whenever an individual with neurofibromatosis begins to suffer from failing vision, a glioma of the optic chiasm is the most likely cause. In addition to impaired vision such tumors commonly produce a swelling of the optic disc and x-ray examination of the optic foramina will usually reveal a dilatation of that bony channel. There may be a defect in the visual fields but it is seldom the precise bitemporal hemianopia which is usually seen with pituitary adenomas which compress the optic chiasm. Often there is a central scotoma or an irregular defect in the visual fields. When the hypothalamus is involved the symptoms are usually drowsiness and lethargy, polyuria, polydypsia and polyphagia, adiposity, and retardation of sexual development. Many of these patients will run a low-grade fever.

Surgical treatment of these tumors is rarely satisfactory. Occasionally they respond to x-ray therapy, at least for a time, but the prognosis is always poor.

Craniopharyngiomas arise from embryonic remnants in the pars tuberalis of the hypophysis on the under surface of the hypothalamus in the region of the tuber cinereum. They are epithelial tumors composed of stratified squamous epithelium. The symptoms to which they give rise are the result of compression of a number of neighboring structures. Because they grow upward and occlude the third ventricle they give rise, particularly when they occur in children, to the signs of increased intracranial tension. This upward pressure also involves the hypothalamus and adiposity, polyuria, and polydypsia, and sexual retardation with atrophy results. Pressure upward and forward upon the optic nerves and chiasma produces a failure of vision and ultimate blindness. It is uncommon with craniopharyngiomas to find the sharp bitemporal defects in the visual fields which are the rule with pituitary adenomas. If the pressure downward upon the hypophysis is greater than that upward on the hypo-

thalamus, a retardation of growth with the production of a pituitary dwarf, precocious senility, and sexual retardation are the outstanding symptoms.

These tumors are microscopically benign and frequently cystic. Nevertheless, they are one of the most difficult of all neurosurgical problems. They are so closely adherent to the undersurface of the hypothalamus that a removal of the tumor without destruction of this important neural mechanism is virtually impossible. As a result these tumors are rarely cured. Evacuation of the cystic cavity may produce a remission of some of the symptoms for a variable number of years, but by and large that is all that one can hope for.

There are of course other neurosurgical lesions which one may encounter and which offer a much more hopeful outlook. There are the occasional benign removable tumors of the cerebrum, and the subdural hematomas. These must never be missed in the mistaken idea that a hopeless neoplasm is present. Cerebral abscesses, too, although now more uncommon, are much more hopeful than before the introduction of chemotherapy.

However, so far as tumors are concerned it is fairly safe to say that brain tumors in children are divisible into two groups: the astrocytomas of the cerebellum, which form about 30 per cent of the entire group and which can be successfully removed in the majority of cases with the patient permanently cured; and the other tumors of the brain, for which little can be done beyond temporary relief.

Pathology of Benign and Malignant Tumors in Childhood

Paul E. Steiner, M.D., Ph.D., Chicago

I. BENIGN TUMORS

The benign tumors of childhood exhibit both quantitative and qualitative differences from those of adults; they are less numerous and the relative proportions of the various types are different. Several explanations may be used to account for these observations. They may reflect merely the slow rate of growth of a tumor so that even if it began before birth or at an early age it does not attain a noticeable size during childhood. Or it may indicate that there has not been lapse of sufficient time for accumulation of and exposure to causative factors, or for such factors to have exerted their effects on the cells through an adequate tumor induction time. Finally, origin from blastomeric inclusions must be given consideration in the mixed and teratomatous tumors, which are relatively commoner in children than in adults. The high incidence of these tumors in the newborn and during infancy and childhood, a period when rapid cell differentiation and growth are occurring, strongly suggests an etiologic relationship to some dysontogeny. If the Cohnheim theory of tumor formation from misplaced embryonal rests has any place today, it is surely in relation to these tumors.

It is difficult to determine the exact size of the problem of benign tumors in childhood because few data are available. Most reports deal only with malignant neoplasms. A few data can be culled from general papers on tumors. A study of the benign tumors found as incidental lesions at necropsy in our own material showed that such tumors are much less common in children than in adults.

Surgical material yields more information. A review was made (at the Children's Memorial Hospital, Chicago, with the kind permission of Dr. Stanley Gibson and Dr. J. P. Simonds) of over six hundred specimens removed surgically from children for diagnosis or treatment. About 22 per cent were malignant tumors which will be discussed in a later paper. About 63 per cent, or nearly two thirds of the specimens, were benign tumors with which we are here concerned. The remainder, about 15 per cent of the total, were non-neoplastic lesions about which more will also be said shortly. The latter group was of special interest because of the difficulty in separating it sharply, in some instances, from the true tumors.

On classifying the benign tumors as to type, it was found that the largest group was composed of polyps papillomas, and polypoid adenomas arising from various epithelial surfaces. Then, in descending order of frequency, the following were found: hemangiomas, dermoids and epidermoids, fibromas, lymphangiomas, nevi, teratomas, lipomas, neurofibromas,

From the Department of Pathology, The University of Chicago.

lipofibromas, chondromas, and osteochondromas. Finally, there was a large group of miscellaneous tumors and tumorlike conditions. These, then, were the benign tumors which the pediatricians encountered most frequently.

The papillary lesions were found most often in the following locations: larynx, rectum, nose, ear, and smaller numbers in a wide variety of locations. Some of these lesions were undoubtedly inflammatory in origin and not true neoplasms as, for example, the nasal polyps. In the case of some of the others the classification is less certain. Many were undoubtedly benign epithelial tumors of adenomatous and other types.

The next largest group of benign tumors, the hemangiomas, were chiefly cutaneous. Visceral hemangiomas as, for example, cavernous hemangiomas of the liver were encountered at necropsy in children less commonly than in adults. These tumors are of special interest because their clinical behavior, which is usually benign, is unlike their histological appearance, which is often suggestive of malignancy. These tumors are composed of a plexis of blood spaces, whose structure may imitate blood vessels of any size and with varying degrees of perfection. In the simplest form they consist of endothelial-lined blood sinuses or capillaries; in their most complex form either arteries or veins may be produced. There are all grades between. These differences explain variations in color, texture, pulsation, and other clinical features. The lymphangiomas were also common. In their extreme form they become the cystic hygroma familiar to all pediatricians.

The mixed tumors formed a large series in which the structure showed increasing complexity, varying from simple epidermoids, which are cystic, through dermoids to teratoids, which may be solid. Some of the latter were malignant. It is often difficult to distinguish the benign from the malignant forms. The distribution of these tumors in the body was very wide. While a few were found in the gonads, the majority were at sites of complex embryologic development such as occurs at the poles of the body, along the spinal axis, and about the face. Their locations as well as their embryonal or complex structure, and their occurrence in young persons give support to their probable dysontogenetic nature. On the proximal, benign end of the spectrum with respect to simplicity in structure were found a number of sebaceous cysts. They are regarded by most observers as not neoplastic, but as simple cysts caused by retention of sebaceous material and desquamated cell debris. They are retained here because on the external surface of the body they can, when they are solitary, clinically resemble small dermoids and cystic teratomas.

The connective tissue tumors formed the third largest group. In descending order of frequency they were: fibromas, lipomas, neurofibromas, lipofibromas, chondromas, and osteochondromas. These tumors showed a wide anatomical distribution. The histologic appearance is indicated by their names. The diagnosis of these tumors with respect to type and degree of malignancy presents the same problems as it does at other ages.

After separating out the three main groups of tumors just enumerated, a large miscellaneous group remained. Over thirty types are represented in this group. Their distribution in the body was equally varied. They illustrate the point that although most of the benign tumors in childhood follow well-established patterns in which some tumors common in adults are poorly represented, nevertheless, sooner or later, almost every type of tumor may be encountered.

In recent years tumors which arise in the endocrine system and exert striking hormonal effects have attracted much attention. In this series such tumors formed an insignificant problem. Similarly, those types of adenomatous hyperplasia which are common in adults where they are believed to be the result of long-standing hormonal imbalances were extremely rare in children.

It may be noteworthy that with one exception the benign tumors, which are most common in adults as incidental findings at necropsy, were not seen in children at all, either in surgical or necropsy specimens. The benign tumors found in a large series of necropsies in adults included large numbers of uterine polyps and fibroids, adenomas of the thyroid, adrenal cortex, and kidney, adenomatous hyperplasia of the prostate, polyps and polypoid adenomas of the colon and stomach, hemangioma of the liver, fibroadenoma of the mammary gland, and

papilloma of the urinary bladder. Of these common types of tumors, only polyps of the colon are more than rare in children. Here is a fertile field for speculation and investigation.

The group of non-neoplastic lesions previously mentioned was of special interest. It was relatively large in proportion to the true tumors, showing that it constituted a real problem in differential diagnosis and treatment. The group is composed of lesions characterized by a mass which grossly may resemble a true tumor. It includes some cysts and pseudocysts, a few masses which are composed of heterotopic tissue and congenital malformations, and many inflammatory polyps. By their size and location these lesions may produce the same clinical effects as do benign tumors. Inasmuch as they present the same problems in clinical diagnosis as tumors, they have been retained in this material for discussion and contrast.

Just as it is sometimes difficult to draw a sharp line between hyperplasia and tumor, so also the distinction between benign and malignant tumors may be difficult. The natural history of each tumor must be known and taken into consideration in making the decision. Some cartilaginous tumors are more malignant than their histologic appearance suggests. Other tumors, including the cutaneous hemangiomas, some nevi, and others are more benign than their infiltrative nature and cell morphology indicate. There are no hard and fast rules to cover these situations; the behavior of each type must be learned.

In summary, the points are made that the benign tumors of childhood exhibit interesting and important peculiarities with respect to total incidence, types, locations, histologic diagnosis, and degree of differentiation from tumors in adults. In children, perhaps more than in adults, benign nontumorous masses exist which enter into differential diagnosis both clinically and pathologically.

II. MALIGNANT TUMORS

The cancers of the newborn, of infants, and of children are of interest to the experimental oncologist as well as to the pediatrician. Although the incidence is lower than it is in adults, tumors at this age are not rare, and as a cause of mortality they now exceed some of the common infectious diseases. Their induction time is, of necessity, short: Whatever the cause of these tumors is, it has only a short time in which to act on normal cells to convert them to cancer cells and thus start the tumors. This alone is sufficient to set the tumors in children apart from those of adults. They are further characterized, however, by their special incidence, locations, types, behavior, and problems in diagnosis and treatment.

The natural history of some of the tumors in children is incompletely known. This is true especially for the rare types. Few physicians have occasion to see enough of them in the course of a lifetime to make adequate observations on diagnosis, course, and treatment on which final conclusions can be based. This gap should now be filled by the Children's Tumor Registry of the Academy.

Incidence.—To obtain an idea of the importance of cancer in childhood, the incidence must be determined. It can be expressed in a number of ways. Thus, it can be stated in terms of the entire population, children in the population, hospital admissions, total tumor deaths, hospital deaths, or necropsies.

The following analysis of incidence was made with data from three sources. These were (a) the Department of Pathology of the University of Chicago; (b) The Children's Memorial Hospital of Chicago (my grateful thanks go to Dr. Stanley Gibson and Dr. J. P. Simonds for permission to make the study); (c) the Board of Health of Chicago (these data were kindly supplied by Dr. Herman Bundesen, President of the Board of Health). The data are of different types and they supplement each other.

In the city of Chicago during 1945 there were reported fifty-one deaths from cancer (excluding neuroblastomas) in the age group of 0 to 9 years, and nineteen deaths in children aged 10 to 14 years inclusive. This constituted a tumor mortality of 12.0 per 100,000 population per year in the earlier age group and 7.7 in the older children. The actual figures are probably higher than those here given because of omission of neuroblastomas and possible other cancers, and because of the negative error in diagnosis inherent in clinical diagnosis not checked by necropsy.

At the Children's Memorial Hospital there were, over a period of years, 116 necropsies on children under 13 years of age with malignant tumors. This was 0.13 per cent of all ad-

missions, 2.49 per cent of all deaths, and 4.14 per cent of all necropsies. The per cent of deaths due to tumor was even higher in the University of Chicago series, probably because of a difference in type and selection of cases, the per cent of intracranial tumors having been higher. In 730 necropsies on children 12 years old or less there were 103 fatal tumors (14.1 per cent). In ninety-seven necropsies on children from 13 to 16 years of age inclusive, thirty (30.9 per cent) had malignant tumors. The necropsy rate at this institution averaged about 80 per cent of all deaths.

Types.—The cancers which occur in childhood are, in many instances, different in type from those of adults. Carcinomas are uncommon, while sarcomas as well as mixed, and embryonal tumors are common. In the combined (Children's Memorial plus University of Chicago) series of 219 malignant tumors in children aged 12 years and under, there was only one carcinoma. This was found in a liver showing juvenile cirrhosis. In adults carcinomas are about ten times as common as sarcomas.

The 116 fatal tumors in the Children's Memorial Hospital series were of the following types: Lymphatic, sixty-three (54.5 per cent); intracranial, sixteen (13.8 per cent); neuroblastoma, eight (6.9 per cent); adenomyosarcoma (Wilm's tumor), seven (6.0 per cent); sarcoma, seven (6.0 per cent); miscellaneous, fifteen (13.0 per cent). The per cent of intracranial tumors in this series was low because many cases had been referred to the University of Chicago where they helped to swell the figures for this disease.

The 103 fatal tumors in the University of Chicago series were of the following types: Intracranial, sixty-three (61.1 per cent); lymphatic, twenty-four (23.3 per cent); neuroblastomas, seven (6.8 per cent); sarcomas, four (3.9 per cent); and miscellaneous, five (4.9 per cent).

In the city of Chicago data, lymphatic tumors were most numerous. They were followed by intracranial tumors, unspecified types, and kidney tumors in that order. Thus, in these three series of tumors the order of frequency of the different types was approximately as follows: lymphatic and hemopoietic (this included leucemia, aleucemic leucemia, lymphosarcoma, and Hodgkin's disease), intracranial, neuroblastomas, renal tumors, miscellaneous sarcomas, and miscellaneous malignant mixed tumors. This is roughly in agreement with the data of others.[1, 2, 3]

The peculiarities of tumors in the young can be accentuated by making a special group of the congenital cases.[4] They can be further emphasized by comparing the cancers in two age groups namely, 1 to 12 and 13 to 16 years. When this was done with the University of Chicago material it was found that while some types (e.g., intracranial and lymphatic) persist in the older group, others (e.g. neuroblastoma) fall off. At the same time, bone tumors, chiefly Ewing's sarcoma, begin to appear. The same features were seen in the city of Chicago data where the division was made at the tenth year. Lung and other tumors appear after this age. Thus, in late childhood the change in types of tumors begins which eventually results in the pattern seen in young adults.

Sites.—Going hand in hand with the peculiarities in type of tumor in children are their differences with respect to location in the body. Some sites and organs which commonly give rise to tumors in children rarely do so in adults, and vice versa. Thus, in 1841, consecutive cancers encountered at necropsy at all ages but mostly in adults the order of incidence, in the ten commonest, was as follows: stomach, intracranial, colon, lymphatic, lung, mammary gland, prostate, pancreas, esophagus, and uterus. Only two of these tumors (intracranial and lymphatic) are common in childhood. The other eight are uncommon, rare, or practically nonexistent (e.g. carcinoma of the prostate). On the other hand, two of the common tumors in children, namely, the neuroblastoma of the adrenal and other sites, and the mixed embryonal tumore of the kidney (Wilm's) are common in adults, although renal carcinomas are not. Hepatoma, or hepatic cell carcinoma of the liver is the commonest carcinoma in children. It is also fairly common in adults. It is the only carcinoma with this double distinction.

Morphology.—Many tumors in children exhibit a dissociation between the degree of their histologic and clinical malignancy. This factor needs recognition for the correct

pathologic interpretation and treatment of these tumors. Some of them are relatively benign appearing, pathologically speaking, but are clinically highly malignant. This is true of many intracranial tumors, some chondromas, and some lymphangiomas. Some of the embryonal and teratoid tumors also fall into this category. Their cells may appear embryonal and immature but not anaplastic, yet metastases may be widespread. On the other hand a few tumors which by histologic criteria should prove to be very malignant, may have a benign course and favorable outcome. Examples of this type of behavior include the cutaneous hemangiomas, and a few of the adrenal neuroblastomas.[1]

Special Pathology.—

A. *Lymphatic and Hemopoietic:* The leucemias are the commonest diseases in this group. Their subclassification is dependent on cytological details and on ideas regarding nomenclature. In general it is believed that in children the blast and lymphatic forms are of relatively greater importance than the myelogenous, and that the acute cases are commoner than the chronic. Both of these observations are the reverse of the situation in adults.

Enlargement of the lymph nodes in the leucemias of childhood is often inconspicuous. This may be true both in the early and the late stages of the disease. At the same time the blood picture may be subleucemic or aleucemic. This, coupled with small lymph nodes which even on biopsy may fail to show striking changes, makes the diagnosis very difficult in such cases, a situation which rarely pertains in adults.

Hodgkin's disease was commoner than lymphosarcoma. This is a reversal of their incidence in adults. The diagnosis of these two diseases by biopsy of lymph nodes during life and by the pathologic findings at necropsy present no unusual problems.

B. *Intracranial Tumors:* The chief intracranial tumors were medulloblastomas, spongioblastomas and astrocytomas. The two former types showed a striking decrease in the 13- to 16-year age group.

C. *Neuroblastomas:* These tumors originate predominantly in the adrenal medulla but, not rarely, in other locations from nervous system elements as well. They form bulky masses in the upper abdomen signalling their presence, or they may first reveal themselves through their metastases, especially those in the skeleton. Most of them occur in the first few years of life. They bear a great clinical resemblance to the embryonal mixed tumors of the kidney (Wilm's) which also form large masses in the upper abdomen in young children. They may sometimes be differentiated by the demonstration of areas of calcification on x-ray examination. The adrenal neuroblastoma is more likely to contain areas of necrosis which calcify than is the kidney tumor. It also has a greater tendency to metastasize early and widely, but this distinction is less reliable.

D. *Adenomyosarcoma of Kidney (Wilm's):* These tumors arise from the kidney where they form large masses. They tend to grow rapidly and to metastasize widely in the abdomen and thorax. They may be congenital or appear in infancy and childhood. They are much less common after puberty. Microscopically they show a mixture of embryonal structures and tissues. Of special interest in association with their structure, age incidence, and possible etiology is the fact that some of these children exhibit developmental anomalies or defects elsewhere in the genitourinary tract.

REFERENCES

1. Farber, Sidney: In Mitchell-Nelson, Textbook of Pediatrics., ed. 4, Revised. Philadelphia and London, 1945, W. B. Saunders Company.
2. Dargeon, Harold W.: Cancer in Childhood, St. Louis, 1940, The C. V. Mosby Company.
3. Schultz, Oscar T.: Abt's Pediatrics, Philadelphia and London, 1926, W. B. Saunders Company, Chap. CXCIII.
4. Wells, H. Gideon: Occurrence and Significance of Congenital Malignant Neoplasms, Arch. Path. 30: 535, 1940.

Bone Tumors

Ralph E. Herendeen, M.D., New York

Tumors of bone are often difficult to diagnose roentgenographically and even with a biopsy the prognosis must be guarded.

Case 1.—Benign tumor of tibia which became malignant. The radiographic diagnosis was a benign giant cell tumor. First curettage showed a benign giant cell tumor but the second curettage showed malignant changes. Even after x-ray treatment and amputation, metastasis occurred and the patient died.

Case 2.—Endothelioma (Ewing's sarcoma) of fibula. There was widening of the medulla and thinning of the cortex. The onionpeel appearance was not characteristic. Involvement of the soft tissues with local heat over the area was present. X-ray treatment showed a good response of the bone tumor but metastasis and death occurred.

Case 4.—Endothelioma of the heal diagnosed radiographically. There was good response to radiation therapy. Amputation was advised but not done. The patient is alive now, which speaks against a diagnosis of a Ewing's sarcoma. It was felt that not cutting into the tumor may have been beneficial in this case.

Case 5.—Fracture through a cystlike area of decreased density. Curettage showed a bone cyst lined with giant cells. X-ray therapy at first caused an increase in size of the cyst, which then later decreased in size.

Case 6.—Giant celled tumor of neck and shaft of femur was diagnosed radiographically. No curettage was done. It improved with x-ray therapy.

Case 7.—Giant celled tumor of radius. This type of tumor grows symmetrically, shows trabeculation, and extends along the shaft of the bone. In children it occurs below the epiphysis but in adults it extends into the joint. Biopsy showed a giant celled tumor. X-ray is the treatment of choice in small doses over several months.

Intracranial Tumors in Children (abstract)

Dr. Stuart N. Rowe, Pittsburgh

Brain tumors occur in children in about one admission out of 700 in our experience on an active pediatric service in a general hospital. This is about in keeping with the experience of others. They make up approximately 17 per cent of the entire group of intracranial tumors in children and adults. The pathology of these neoplasms varies widely, but the majority are gliomas occurring in the posterior cranial fossa. Another important group are the craniopharyngiomas, growing in the suprasellar region.

The clinical picture of brain tumors is characterized primarily by symptoms of increasing intracranial pressure, including bouts of morning vomiting and morning headache, impairment of vision, and apathy and drowsiness. In some instances, slight focal neurologic changes including incoordination of hand movements and staggering gait may point to a cerebellar lesion. In the suprasellar group, endocrine changes may be apparent and x-rays frequently disclose intracranial calcification. Enlargement of the head and the positive Macewen's sign on percussion is an early and very helpful clinical finding. Changes in the optic discs varying from 1 to 6 diopters of papilledema are common. When the diagnosis is suspected, careful neurologic studies and ventriculogram are usually needed to establish the exact diagnosis and localization of the lesion. Surgical treatment is effective in the majority of patients and in a few, x-ray therapy offers marked relief over a period of months or years.

A. *Pathology* varies greatly

All malignant tumors invade, become adherent, and extend into surrounding tissues, but usually do not metastasize.

1. Benign tumors
   - Meningioma
   - Craniopharyngioma
   - Epidermoid
   - Astrocytoma
   - Pinealoma
2. Malignant tumors
   - Medulloblastoma
   - Spongioblastoma
   - Sarcoma

B. *Clinical picture*

It may be difficult to recognize tumors early because the child is less likely to describe symptoms accurately, is less likely to complain, and the skull is less elastic than in the adult.

1. Intercranial hypertension
   a. Vomiting—occurs early in the morning, is projectile, is not accompanied by much nausea, may be intermittent, lasting for three to four days at a time, and there is an absence of other gastrointestinal symptoms.
   b. Headache—not clearly defined, but usually more in the morning, associated with vomiting, and most often frontal but occasionally occipital and nucal.
   c. Impaired vision—may extend to complete blindness. There is gradual onset, often with double vision or photophobia.
   d. Lethargy and loss of drive may be present. Mental changes may be mild.

C. *Physical findings*

1. Head
   a. Often enlargement of head, general or local.
   b. Veins often prominent.
   c. McEwen's sign present.
   d. Choked disc usually present, but not always.
   e. Strabismus due to involvement of sixth nerve causing paralysis of external rectus.
2. Focal neurologic changes
   a. Cerebellar tumors—may be no changes; usually awkwardness, stumbling, and staggering. Uncoordinated use of hands. Positive Rhomberg. Some myotonia, and reflexes are absent or sluggish. Usually little increase in pressure when brainstem is involved.
   b. Supratentorial
      (1) Craniopharyngioma—increased intercranial pressure, changes in visual fields, endocrine changes such as diabetes insipidus, and often intercranial calcifications.
      (2) Pinealoma—endocrine changes such as precocious sexual development and impairment of eye movements.
   c. Cerebral hemisphere tumors—motor changes, speech difficulty, epilepsy, and sensory changes.
3. Additional diagnoses
   From x-ray of the skull
   Visual field examination
   Spinal puncture
   Encephalogram
   Electroencephalogram

D. *Treatment*

Depends on pathology, location, and size of tumor. Surgery offers most cures in such tumors as astrocytomas, craniopharyngiomas, ependymomas, and meningiomas. X-ray treatment and surgical relief of pressure in medulloblastomas and spongioblastomas.

DISCUSSION

DR. DARGEON.—I would like to ask about the terminology of benign and malignant tumors. Is there any definite criterion to differentiate the two—would it not be better to talk about benign and malignant cancer? The general practitioner may be confused with technical names of tumors.

DR. STEINER.—That would not be good because of the stigma attached to the term cancer. It would seem better to use the general term neoplasm.

DR. DARGEON.—But all tumors are not new growths.

DR. DOROTHY H. ANDERSON, NEW YORK, N. Y.—It is difficult to differentiate early neuroblastoma from leucemia. Small tumors are often not felt and one must wait for bone

metastasis. Bone marrow smears at times are difficult to differentiate into specific cell groups. Often nothing shows up in the blood stream early.

DR. STEINER.—I agree with you. Sternal punctures may be misleading.

DR. DARGEON.—One must use clinical, laboratory, and radiographic findings together for diagnosis.

DR. BIGLER.—The malignancy of lymphoma and stages up to lymphosarcoma is extremely hard to differentiate from biopsy. A tumor may appear very malignant and yet not metastasize or recur.

DR. STEINER.—Calcification occurs in neuroblastoma and not in Wilm's tumors.

DR. HERENDEEN.—I have seen calcification in Wilm's tumors, especially following radiation.

DR. DARGEON.—That may be due to hemorrhage.

DR. STEINER.—Two-thirds of fatal tumors occur in childhood.

DR. HERENDEEN.—Dr. Rowe, is there any significance in an absence or an increase in vascular marking in skull x-ray films?

DR. ROWE.—It depends upon the age of the child. They are not so pronounced until after 15 years of age. They give no significance as to the location of the tumor.

DR. DARGEON.—The diagnosis of bone tumors should not be made by x-ray alone or by test doses of x-ray. Biopsy should be done. The differentiation even then between chronic osteomyelitis and endothelioma may be exceedingly difficult.

DR. G. D. JOHNSON, SPARTANBURG, S. C.—Does treatment offer any hope for lymphoblastoma?

DR. DARGEON.—There are "five-year cures" of lymphosarcoma reported. We have one case that has survived six years. Five years is not a long enough period for a cure to be considered. The child should remain well for at least ten years. I have seen children free of symptoms of various types of cancers for seven or eight years who later succumb to the disease.

DR. BUCY.—The term "five-year cure" is merely a handle. Everyone has seen recurrence of cancer of the breast after the five-year period. In melanosarcoma we have seen metastases after twenty-five or thirty years. Five years is the arbitrary term but a useful one.

DR. STEINER.—What is the lining of the cyst which is associated with astrocytoma?

DR. BUCY.—Ordinarily it is not lined. There is a glial scar. It is important to search for the tumor when emptying the cyst.

DR. JOHNSON.—Is the earliest sign in intracranial tumors in children usually intracranial pressure?

DR. BUCY.—Usually.

DR. DARGEON.—Will you please give the differential diagnosis between lead encephalopathy and brain tumor.

DR. BUCY.—This can be very confusing. Sixty years ago the elder Dr. Bramwell said he never made the diagnosis of brain tumor without considering lead encephalopathy. In the glass and pottery industries at that time it occurred fairly frequently. It is still seen in children because they will eat anything. I have known them to lick the paint stick out of the painter's bucket. They may get it from eating painted plaster. It is sometimes acquired from using storage batteries as fuel. Toys are not often the cause now because of a change in the nature of the paint used. The chief symptoms of midline cerebellar tumors in children are staggering and increased intracranial pressure. There is marked cerebral edema in lead poisoning, which gives increased intracranial pressure, and there

often is staggering. There are two points very important in the differential diagnosis: (1) Convulsions are generally present in lead encephalopathy, rarely in brain tumors in childhood; (2) x-ray demonstration of the lead lines at the epiphyses of the long bones. These do not become demonstrable for some time after exposure. This x-ray point of differentiation cannot be used in adults. Of course, in children as well as adults there may be present other signs of anemia, stippling of the red cells, or a lead line on the gums (only found in association with carious teeth and infection around the gums). Peripheral neuritis is rare in children.

DR. DALE.—Have you seen many intracranial dermoids?

DR. BUCY.—Intracranial dermoids grow so slowly that ordinarily symptoms are not present until adolescence or adult life. Intraspinal dermoids may give rise to symptoms earlier as there is less room in the spinal canal and the spinal cord cannot adapt itself to compression as can the brain.

DR. H. S. BERMAN, DETROIT, MICH.—Do you consider encephalography dangerous if used for diagnosis when the operator is not prepared to do a trephine of the skull?

DR. BUCY.—It is not very helpful in diagnosing brain tumors in children as there is ordinarily some obstruction of the ventricular system which interferes with adequate visualization; also, it is dangerous. A child with intracranial pressure may get a herniation of the cerebellum through the foramen magnum. Even following lumbar puncture done with care and withdrawing only 5 or 10 c.c. of spinal fluid in cases of brain tumor, fatalities do occur, although they are not numerous. In encephalography, 50 or 60 c.c. of spinal fluid may be withdrawn.

DR. BERMAN.—Do not many brain tumors grow to the point where they are fatal without being diagnosed?

DR. BUCY.—Encephalography may be done in other conditions, such as atrophic lesions and a convulsive state, but not where there is reason to suspect a cerebellar tumor.

DR. BERMAN.—Do you think that many cases seen by doctors have a delayed diagnosis because of failure to do early encephalography?

DR. BUCY.—I do not think so.

DR. RUTH M. BAKWIN, NEW YORK, N. Y.—Does craniopharyngioma give any symptoms in the pharynx?

DR. BUCY.—Rarely. Several tumors, most commonly cancer, may invade the base of the skull from the nasopharynx. In a few very rare cases, craniopharyngiomas have eroded the sphenoid bone and protruded into the nasopharynx.

DR. JOHNSON.—Do you see many cases of undescended testicles which have undergone sarcomatous change?

DR. STEINER.—Changes in cryptorchidism are likely to occur later in life. The occurrence of sarcoma in testicles lying outside of the scrotum is twenty times as great as in the testicles lying in the scrotum.

QUESTION?

What is the prognosis in cystic hygroma?

DR. DARGEON.—The prognosis in cystic hygroma is good if operative procedures can be performed successfully. The technical difficulties may be great. It may extend well up into the neck or far down into the chest. Often surgeons have a transfusion started before operation because they do not know whether it will turn out to be a simple procedure lasting half an hour or a complicated procedure lasting two or three hours.

(Dr. Dargeon showed a picture of a retinoblastoma and stated that unilateral cases were treated by enucleation.)

DR. BUCY.—I remove the optic nerve also, as the tumor often invades the nerve.

DR. STEINER.—Do you sterilize these children? It is considered hereditary.

DR. DARGEON.—There have been cases reported where the progeny did not have it.

Academy Proceedings

REPORT OF THE MEETINGS OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

PITTSBURGH, PA., FEB. 23, 1947

Abstract of Proceedings

A meeting of the Executive Board of the American Academy of Pediatrics was held in the Hotel William Penn, Pittsburgh, Pa., Sunday, Feb. 23, 1947. There were present Drs. Durand, Beavens, Stringfield, Hill, Kennedy, Munns, Spickard, Quillian, Bruce, Martmer and Grulee, and, by invitation, Dr. James Wilson. The meeting was called to order by the President, Dr. Jay I. Durand.

The report of the Treasurer was presented. It was moved by Dr. Stringfield, seconded, and carried that the present budget be carried over until the meeting of the Executive Committee on July 7-8.

The next order of business was the reports of Committees.

Dr. George M. Wheatley reported for the Committee on Rheumatic Fever. It was moved by Dr. Hill, seconded, and carried that the Committeee consider the advisability of setting up state rheumatic fever committes to carry its objects in the various states.

Dr. James G. Hughes reported for the Committee on Cooperation with the American Legion. It was moved by Dr. Hill, seconded, and carried that Dr. Hughes be asked to keep in touch with the American Legion's (Child Welfare Division) and, in case his presence at meetings is necessary, that his expenses be paid by the Academy.

The Secretary read a letter from Dr. Harold Mitchell concerning rural school health. It was moved by Dr. Hill, seconded, and carried that the Secretary write a letter to Dr. Mitchell, stating that his report had been read with great interest, but it was the feeling of the Executive Board that before any definite action is taken, more information on the problems involved should be made available to the members of the Executive Board.

Drs. Kerlan and Stormont of the Food and Drug Administration discussed the question of cooperation with the Academy on drugs. It was moved by Dr. Kennedy, seconded, and carried that a committee be appointed by the President to cooperate with the Food and Drug Administration on problems relating to pediatrics.

The report of the Tumor Registry was presented by Dr. Harold W. Dargeon.

The Secretary read a letter from Mr. Rose of Mead Johnson and Company enclosing a check for $25.00 for child nutrition. This money, with $24.00 already on hand, will be allowed to accumulate.

The Secretary read a letter from Dr. Bret Ratner regarding a Committee on Allergy of the American Academy of Pediatrics. It was moved by Dr. Hill, seconded, and carried, that the Secretary inform Dr. Ratner that the Executive Board approves his idea and that he be appointed chairman of a committee to get things organized and report back at the next meeting.

The Secretary read a letter from Mr. Walter A. Taylor, Director of Department of Education and Research, the American Institute of Architects. The Secretary was instructed to write Mr. Taylor telling him the Academy would cooperate in any way possible.

Dr. Stringfield reported that he had communicated with Mr. Hutchinson concerning the National Conference on Family Life. This organization is planning a White House Conference on Child Life in 1948.

Dr. Martmer reported on the proposed library and museum of pediatrics. He showed plans of the proposed building and discussed approximate costs. It was moved by Dr. Hill, seconded, and carried that the idea of the plans be approved and the Committee continued.

Dr. Martmer read a letter from the architect who had drawn up the plans. It was moved by Dr. Stringfield, seconded, and carried that a letter of thanks be sent to the architect for what he had done, and explaining that in the event such a building is contemplated that his firm as architects and engineers will have the first consideration.

Dr. Sisson for the Committee which had been appointed to investigate and make suggestions about future policies in regard to a public relations counsel and distributed to the members a copy of the report made by Mr. John C. Gourlie, whom the Committee had interviewed.

Dr. Hubbard presented the following resolutions in recognition of the cooperation which has been received from the various organizations to make the Study at least a partial success:

Whereas, one year has now passed since the American Academy of Pediatrics Study of Child Health Services was launched on nationwide scale;

Whereas, the Academy of Pediatrics has been able to develop and conduct this Study on a much larger and more far-reaching scale than had originally been anticipated or than would have been possible without the support of the United States Public Health Service, the United States Children's Bureau, the National Foundation for Infantile Paralysis, the Field Foundation, and those commercial firms listed below;

Whereas, the cooperation of Academy, the United States Public Health Service, and the Children's Bureau has establishd an effective working relationship between two Government agencies and the Academy of Pediatrics and has set the stage upon which similar cooperation may continue in implementing the results of this factfinding Study;

Resolved, that the American Academy of Pediatrics express to the Surgeon General of the United States Public Health Service and to the Chief of the Children's Bureau its appreciation for their continuing support;

Resolved, that the Academy of Pediatrics express its gratitude for the contributions received from the National Foundation for Infantile Paralysis and request the National Office to extend this expression of appreciation to the County Chapters whose support has been essential for the development of State Programs;

Resolved, that the Academy express its gratitude for the contributions received from the following commercial firms who have made generous financial contributions to the Central Office of the Academy Study:

Mead Johnson Company	Borden Company
Pet Milk Company	Lederle Laboratories
Carnation Company	Mennen Company

M and R Dietetic Laboratories

Resolved, that the foregoing resolutions be incorporated in the minutes of the Executive Board of the Academy of Pediatrics held at the William Penn Hotel, Pittsburgh, Pa., Feb. 23, 1947, and that a copy of these resolutions be sent to all those named herein.

Respectfully submitted,
EXECUTIVE BOARD

It was moved by Dr. Stringfield, seconded, and carried that these resolutions be adopted.

The approaching Pan-American Congress was discussed by Drs. Grulee and Hurtado and, by invitation, Drs. Ong and Nicholson of Washington, D. C. The program was presented, the plans for entertainment discussed, and an approximate budget for the expenses of the Congress outlined. A letter was read from Dr. Henry J. Klaunberg, President, Washington Institute of Medicine, regarding publishing the proceedings of the Congress in the Quarterly Review of Pediatrics. It was agreed that this be done and Dr. Grulee said he would like the same thing to appear in the JOURNAL OF PEDIATRICS. After a discussion of the cost of the Congress, and the approximate budget, it was moved by Dr. Spickard, seconded, and carried that the Treasurer make up the deficit from the Academy funds, with the understanding that if there is an assessment for the International Congress, 25 per cent of it will go toward making up the deficit on the Pan-American Congress.

The Secretary read a letter from Carlos Ferrufino of the Sociedad Boliviana de Pediatria.

At the evening session there were present, by invitation, Drs. John A. Anderson of Salt Lake City, and Hugh L. Moore of Dallas, Texas, the editors of the JOURNAL OF PEDIATRICS, and Drs. Hansen, Butler, Faber, Powers, McIntosh, McQuarrie, and Stokes of the editorial board.

Dr. Anderson discussed the facilities for holding a meeting in Salt Lake City. It was the consensus of opinion that a Region IV meeting or a sectional meeting be held in Salt Lake City on September 8, 9, and 10, 1947.

Dr. Moore presented an invitation from Dallas to hold the 1947 annual meeting there. It was moved, seconded and carried that the annual meeting be held on December 8, 9, 10, and 11 in Dallas, Texas.

The question of whether members granted leaves of absence should be catalogued with regular members, received all correspondence, or should be put in a separate category was discussed. It was decided that they should be listed separately with their last known address.

It was moved by Dr. Beaven, seconded and, carried that the initiation fee be increased to $50.000 on applications received on or after July 1, 1947.

The Secretary read a letter from Dr. Herbert Coe concerning the establishment of a Surgical Fellowship, or Affiliate Fellowship or Surgical Affiliate to cover the admission of men devoted to the study of the surgical problems of infancy and childhood. In the discussion it was stated that in other specialties, such as Allergy and Dermatology, there are men devoting their entire time to diseases of children in these branches. It was moved by Dr. Beaven, seconded, and carried, that a committee be appointed to look into this matter and report at the next meeting. The Chair appointed Drs. Beaven and Munns as the Committee.

There being no further business, the meeting adjourned at 9:50 P.M.

PITTSBURGH, PA., FEB. 26, 1947

Abstract of Proceedings

A meeting of the Executive Board of the American Academy of Pediatrics was held in the Hotel William Penn, Pittsburgh, Pa., Wednesday, Feb. 26, 1947, following the annual business meeting. There were present Drs. Hill, Pease, Bruce, Munns, Spickard, Beaven, Stringfield, Hurtado, Martmer, Kennedy, Toomey, Barba, McElhenney, Hubbard, and Grulee. The meeting was called to order by the President, Dr. Lee Forrest Hill.

The first order of business was the consideration of the proposed changes in the by-laws to be acted upon next July. These changes, which will be necessary to instrument the changes incident to the adoption of the plan for redistricting, were discussed and will be submitted to the membership for vote before final action of the Executive Board in July.

It was recommended that the funds remaining in the former Regions be turned over to the Secretary's office with the provision that they be used for any emergency arising, upon recommendation of the Executive Board.

The Rheumatic Fever Committee recommended that the Academy mail a pamphlet on rheumatic fever to each member. This recommendation was approved.

The corrected recommendation of the Committee on the Study of Child Health Services were approved. A Committee consisting of Drs. Stringfield, Hubbard, Sisson, and Grulee was suggested to study the question of publicity, both for the Study and the Academy, and report at the July meeting of the Executive Board of the Academy.

A committee consisting of Dr. Herbert E. Coe as Chairman and Dr. Beaven, was appointed to investigate and report back to the Executive Board at its meeeting in July the possibility of enlarging the scope of the membership to include men in allied branches of medicine who were confining their work to children.

A letter from Dr. Henry Poncher regarding the papers on the Rh factor was discussed, and it was decided to ask Dr. Poncher to contact Dr. Diamond about the preparation of a monograph to be distributed to the members of the Academy, the Academy to be responsible for distribution but not for financing publication.

On motion duly made and seconded the meeting adjourned at 6:55 P.M.

FIFTEENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

PITTSBURGH, PA., FEB. 24, 25, 26, AND 27, 1947

ANNUAL BUSINESS SESSION

The annual business session of the American Academy of Pediatrics was held in the Hotel William Penn, Pittsburgh, Pa., on Wednesday, February 26, 1947. The meeting was called to order at 2 P.M. by the President, Dr. Jay I. Durand.

The first order of business was the presentation of the 1947 Awards by Dr. Joseph Stokes, Jr.

DR. STOKES.—The Mead Johnson Award is presented yearly at the national meeting of the American Academy of Pediatrics to that pediatrician of 35 years or under who, in the opinion of the Committee on Awards of the Academy, has carried out the most distinguished investigations in his chosen field.

The membership of the Academy will remember that at the last annual meeting in Detroit no Mead Johnson Award was presented. The inability of the Committee to select a suitable recipient for that occasion lay primarily in the enlistment of a major portion of young investigators in the armed services. For this and many other obvious reasons it has appeared appropriate to the Committee that any distinguished work emanating from such younger men in the armed services deserved recognition over and above that work of young investigators who did not have the opportunity of serving in a similar capacity. Also the Committee felt that if work of sufficient value had been conducted over the war period in the armed services by more than one individual, and if the Mead Johnson Company concurred, an award should be made retroactively for the year 1945, as well as for the year 1946. Such work of sufficient value was found, and such concurrence by the Mead Johnson Company was obtained.

The award for 1945 will be presented by a member of the Committee on Awards and the recipient's former teacher, Dr. Grover F. Powers.

DR. POWERS.—The recipient of this Award made a distinguished contribution to the war efforts and to preventive medicine in the control of malaria in the South Pacific area from July, 1942, to December, 1944; he later served as acting chief of Preventive Medicine at the beginning of the Okinawa campaign and at headquarters of the Pacific Armed Forces. His comprehensive, confidential report to the Surgeon General served as an inspiration and model for other workers in the field.

The commanding officer, General Earl Maxwell, states that the recipient "began his work on Malaria, as Epidemic Disease Control Officer, at a time when combat conditions in Guadalcanal on the New Hebrides Islands had taken a terrific toll of military personnel. Although there was considerable actual combat, there were eight malaria cases for each combat admission to the hospital. He quickly and efficiently planned and carried out control measures, and effectively lowered malaria and other epidemic disease conditions to a degree where there were practically no new cases contracted in our troops. Within one year on Guadalcanal, malaria rates were reduced to 1/200 of what they had been when he and his subordinates started his intensive campaign against this disease.

"The recipient's tireless energy, his scientific knowledge, and his dauntless courage in pioneering the scientific investigations of tropical medical subjects in the face of severe climatic and other obstacles were an inspiration to all officers and men who served under him. His inquisitive searching and thorough method of attack always created incentive for new knowledge of tropical diseases. His observations and lessons learned were submitted to higher headquarters without delay and were very helpful in planning for further combat missions on the Pacific Islands."

The recipient was for some time resident in pediatrics in the New Haven Hospital and instructor in pediatrics in the Yale University School of Medicine, where he was trained

in clinical epidemiology under the late Dr. James D. Trask. He was a successful practitioner of pediatrics prior to entering on active duty with the Army of the United States as a major with the 39th General Hospital (Yale Unit) and reverted to inactive status four years later with the rank of Colonel. The recipient earned four campaign stars and the bronze star medal to which was added the Oak Leaf Cluster one year after the first citation. His career in the Armed Forces furnishes another inspiring example of the role pediatricians play in military medicine and in the broad field at public health.

The Committee on Awards of the American Academy of Pediatrics in behalf of the Academy takes great pleasure in presenting the Mead Johnson Award of 1945 to Paul Alwain Harper.

DR. HARPER.—Mr. President, Mr. Chairman, and Fellows of the Academy: I wish to express my deep appreciation to the American Academy of Pediatrics for the bestowal of its Mead Johnson Award. In a large sense the honor means that work of this kind does not belong to any individual but is the result of combined efforts of many individuals who are too numerous to mention. The paper which I wish to present at this time will show the attempts by all these groups to solve these problems.

(*Reads paper.*)

DR. STOKES.—The recipient of the Mead Johnson Award for 1946, even during his undergraduate years in the School of Medicine, University of Pennsylvania, showed a distinct aptitude for and a growing interest in the field of medical research. Studies on vitamin D begun during his first and second years were of such significance that he became the recipient at this early period of a first prize award from the School of Medicine for investigations conducted by undergraduates.

During his later clinical hospital training, both at the University of Pennsylvania and under Dr. Edward A. Park at Johns Hopkins Medical School, there was never a time in which he was not conducting able investigations bridging the gap between the laboratory and the patient.

His interest and aptitude for research were strengthened and deepened by two years spent at the Rockefeller Institute for Medical Research with Dr. Leslie Webster, at which time he initiated the use of ultraviolet light for inactivation of rabies virus, a method now used widely in rabies vaccines.

Following his return to Johns Hopkins Medical School he soon was appointed Medical Director of the Sydenham Hospital, where his continued investigations of infectious diseases are familiar to all of us.

When World War II started, he soon became a member of the Commission on Measles and Mumps, Army Epidemiological Board, and later, as a result of a greater opportunity to work with the armed services in the field, he joined the Naval Medical Research Unit No. II, which conducted outstanding investigations centering around Guam during the latter part of the war.

During this war period, in addition to the quality of the work which he will outline to some extent this afternoon, he has indicated his desire and ability to assist wherever his demonstrated talent would count the most.

The Committee on Awards of the American Academy of Pediatrics therefore on behalf of the Academy takes great pleasure in presenting to Dr. Horace L. Hodes, Associate Professor of Pediatrics, Johns Hopkins Medical School, and Medical Director, Sydenham Hospital the Mead Johnson Award for 1946.

DR. HODES.—Mr. President, and Members of the Academy: I should like to express my appreciation to the Academy for the Mead Johnson Award for 1946.

(*Reads paper.*)

DR. STOKES.—In contrast to the Mead Johnson Award, given chiefly for stimulation of younger men or women for research work, The Borden Award permits the Committee a greater latitude of choice. It has no age limit. It is awarded for distinguished work in the field of nutrition.

The citation of this Award will be presented by a grateful and admiring pupil of the recipient, Dr. Allan M. Butler, Professor of Pediatrics, Harvard University Medical School.

DR. BUTLER.—This Borden Award of 1946 is made for experimental studies consistently pursued over the past thirty years on the anatomy of the body fluids and maintenance of concentrations such as sustain the nutrition and function of tissue cells under the vicissitudes of disease.

Studies characterized by a perception, definitiveness, and such scientific significance as to have given the unusual honor to a pediatrician of membership in the National Academy of Science.

Studies conducted by an individual whose breadth of understanding is reflected in the quality of this humor; whose stimulation to and esteem by younger pediatricians are indicated by his being the first president of their Society of Pediatric Research; whose clarity of thought and artistry of exposition has resulted in his lecture syllabus becoming a standard text of undergraduate students, physiologists, and physicians; whose example in clinical investigation, in editing a medical journal and in teaching, has set standards for American Medicine of which his fellow pediatricians are justly proud.

The Committee on Awards of the American Academy of Pediatrics, on behalf of the Academy takes great pleasure in presenting to Dr. James L. Gamble, Professor of Pediatrics and Chairman of the Department of Pediatrics of Harvard University Medical School, the Borden Award of 1946.

DR. GAMBLE.—I am quite unable to find words which will adequately express my appreciation of this large honor from the Academy and to find something suitable to say to the Borden Company is equally difficult. I am astonished to think that the Borden Company would give this award to a pediatrician who believes, for instance, in water and electrolytes. That they are willing to make the Award to such an individual seems to me to indicate the most extraordinary graciousness.

As regards Dr. Butler's kind words, I am sure you will understand that a person has reached the highest pinnacle of gratification when Dr. Butler's words are kind. I say this because Dr. Butler has long been my helpful and my severe critic.

The talk that I was asked to prepare for this meeting is entitled, "Deficits in Diarrhea."*

THE SECRETARY.—The following men and women have been accepted for active membership:

Region I

Herman Anfanger, New York, N. Y.
Samuel B. Hurwich, Toronto, Ont.
Theodore Hunt Ingalls, Southboro, Mass.
Harvey Leinbach, Reading, Pa.
William C. McCarthy, Pittsburgh, Pa.
Rafael R. Muniz, New York, N. Y.
Robert D. Nix, Sewickley, Pa.
Donald Ross Reed, Tarrytown, N. Y.
Lewis J. Schloss, North Plainfield, N. J.
Austin H. Schoen, Brooklyn, N. Y.
Harry M. Sternberg, Brooklyn, N. Y.
Dwain Newton Walcher, New Haven, Conn.
David L. Weinstein, Washington, D. C.

Region II

Fred S. Brooksaler, Dallas, Texas
Alphonse Louis Girardin, Jr., Fort Myers, Fla.
Angus M. McBryde, Durham, N. C.
William Lucas Venning, Charlotte, N. C.

*Published on page 488 of the May, 1947, issue of the JOURNAL.

Region III

Lawrence Breslow, Chicago, Ill.
James P. Conway, Shorewood, Wis.
Sol Paul Ditkowsky, Chicago, Ill.
James William DuShane, Rochester, Minn.
A. R. Eveloff, Lake Springfield, Ill.
Max Miles Ginsburg, Denver, Colo.
Bernard Gumbiner, Chicago, Ill.
Harry C. Metzger, Detroit, Mich.
Helen Seibert Reardon, Ann Arbor, Mich.
Justus B. Roberts, Ottumwa, Iowa
Arthur H. Rosenblum, Chicago, Ill.
Herschel Sachs, Cincinnati, Ohio

Region IV

Talcott Bates, Monterey, Calif.
Norman Ward Clein, Seattle, Wash.
Alexander Hatoff, Oakland, Calif.
William W. Ornduff, Berkeley, Calif.
Lawrence E. Reck, San Diego, Calif.
James T. Stanton, Bakersfield, Calif.
Chieh Sung, San Francisco, Calif.
John Charles Wilcox, Claremont, Calif.

Region V

Milton Carlow Braga Netto, Rio de Janeiro, Brazil
Amador Guerra y Sanchez, Habana, Cuba
Rafael de la Portilla, Lavastida, Habana, Cuba
Enrique Galan Conesa, Habana, Cuba
Lorenzo Exposito Martinez, Habana, Cuba
Antonio Carbonell Salazar, Habana, Cuba
Alfredo Ceballos Carrion, Guayaquil, Equador
Pedro J. Alvarez, Caracas, Venezuela
Lya Imber de Coronil, Caracas, Venezuela
Guillermo Tovar, Caracas, Venezuela

The following requests for Emeritus membership were accepted by the Executive Committee:

Clara E. Hayes, Washington, D.C.
Charles Kimball Johnson, Burlington, Vt.
Martin D. Ott, Davenport, Iowa
Robert A. Strong, Pass Christian, Miss.

The resignation of Dr. John E. Gordon, Boston, Mass., was accepted and Dr. R. R. Struthers, New York City, was granted a year's leave of absence.

It is the unfortunate duty of the Secretary to report to you the deaths that occurred since the last report.

James L. Foster, Pittsburgh, Pa.
Justin A. Garvin, Shaker Heights, Ohio
Ralph E. Pray, Salinas, Calif.
Jose Robalinho de Oliveira, Pernambuco, Brazil
William Ewing Sinclair, Orlando, Fla.
Charles E. Turcot, Quebec, Que.
Henry P. Ledford, Wichita Falls, Texas

The Vice-President, Dr. Lee Forrest Hill, then took the Chair and the President presented his report.*

*Published on page 485 of the May, 1947, issue of the JOURNAL.

THE PRESIDENT.—The next item of business will be the reports of Committees. Dr. Joseph Wall will report on pending legislation for the Committee on Legislation.

Report of the Committee on Legislation

The Hill-Burton Bill, formerly S.191, passed the Seventy-Ninth Congress and is now known as the Hospital Survey and Construction Act of 1946.

Appropriations were made available for State surveys and authorized, but not appropriated, for construction of hospitals and health centers. It is to be hoped that members of the Academy will interest themselves in proposed health facilities for children through advice to and consultation with the various State agencies entrusted with the implementation of this Act. Their aid in selection of localities for child health facilities and in the planning of such should be welcomed by the communities concerned, more especially as in the near future the results of the Survey by the Academy's Child Health Services Study Committee should be at least partly available, as the Director assures us, which would aid in delineating health needs of children in the various states.

S.545, known by the patronymic of the Taft health bill, was introduced in the Senate on February 10, 1947, by Senator Taft (for himself, Mr. Smith of New Jersey, Mr. Ball of Minnesota, and Mr. Donnell of Missouri) and referred to the Committee on Labor and Public Welfare, the new designation of the Committee on Education and Labor, under the reorganization act.

Physicians in general, as well as pediatricians, should be interested in the provisions of this bill, which establishes a National Health Agency by congressional enactment and not by presidential order.

All activities of the Federal government, excepting those of the armed forces and the Veterans' Administration, are to be centralized under this bill. The Health Agency is to be headed by a physician. (Dr. Wall explained the salient features orally.)

S.140, introduced by Senators Fulbright and Taft, proposes the establishment of a new department in the Federal Government of "Health, Education and Security," providing a secretary who shall have cabinet rank.

Under this bill, hearings having been posted for February 28, by the Committee on Expenditures in the Executive Departments, there would be placed a lay intermediary between the health division and the President. Matters of health would be in charge of an Under-Secretary of Health, a physician, of co-equal rank with the Under-Secretary of Education and the Under-Secretary of Security, the latter word replacing the word "Welfare" which appeared in former bills. The Fulbright-Taft bill is largely sponsored by educators and social uplifters who would, no doubt, dominate the Federal structure to be created by the proposed act.

H.R.1980, introduced in the House a few days ago by Representative Howell of Illinois, formulated and sponsored by Mr. George J. Hecht, owner and publisher of *Parents' Magazine*, proposes expansion of funds for school health purposes to be administered by the Children's Bureau. For the first year 12 million dollars is the appropriation named.

As originally planned, this bill proposed enlargement of funds of Title V of the Social Security Act, as amended, by adding to part 4 of Title V the measures in behalf of school health services as proposed by Mr. Hecht and his associates.

In the early construction stages of this bill, the purposes of providing additional funds to be expended under existing statutes, where need could be shown, seemed to be in line with the policies expressed by the Academy at its Detroit meeting, but after numerous consultations by the sponsor with Federal officials, educational authorities, labor representatives and many others, the proposed bill emerges quite unlike the original draft. In fact, the bill as introduced represents the seventh draft modified by various interests.

The participation of educators in school health matters would seem to place unusual power in the hands of those who are neither qualified nor entitled to exercise any degree of dominance in matters affecting the health of children.

The Hecht bill as introduced proposes that the National School Health Services Act be made a separate entity and it is not now proposed as an amendment to existing statutes as incorporated in the Social Security Act.

Because of its actual introduction only a few days ago, the Committee on Legislation has not had time nor opportunity to report favorably or unfavorably on this measure, but will give to it early consideration, with the assistance of Dr. Harold Mitchell, chairman of the Committee on School Health.

Respectfully submitted,

JOSEPH S. WALL, Chairman
FRANK VAN SCHOICK
HARVEY F. GARRISON
W. L. CRAWFORD

THE PRESIDENT.—We have a small surprise for Dr. Wall. All of us appreciate the amount of time Dr. Wall has given to this Legislative Committee and the skill with which he handled it. As an expression of our appreciation the Executive Board has had an illuminated scroll made to present to Dr. Wall. This is the first time that such an honor has ever been given by the Academy. I should like now in recognition of his services, far beyond the call of duty on Dr. Wall's part, to present this citation on the part of the Academy.

DR. WALL.—Mr. President and Members of the Academy: This comes to me as a complete and absolute surprise, for I did not know I was included among the Oscars that have been distributed this afternoon. I deeply appreciate this action on the part of the Committee. I feel it is not due to me, for I did only what every member of the Committee would do if given the job. I am greatly appreciative of this honor.

THE PRESIDENT.—The next item will be the vote on redistricting.

DR. MARTMER.—I will throw on the screen two slides: one a map, showing the states to be included in the redistricting, and the second, giving the number of states in each district with the number of members of the Academy in each district.

While there is a considerable amount of territory in the extreme West and in Region VII, the number of pediatricians in each area who are members of the Academy at the present moment is appreciably equal, and that is the plan, based on an equal representation on a numerical basis.

THE SECRETARY.—I have requested this plan in order to have a fair representation. As it is now, the man on the West Coast has the same amount to say in the Academy of Pediatrics' Executive Board as any five men on the East Coast, and as any three or four men in the Middle West and any two men in the South. This new distribution does not separate the old groups from the standpoint of meetings. Meetings will be held as they have been in the past, but the responsibility for those meetings would be distributed according to the number of members.

DR. H. LESLIE MOORE.—I move that the report be adopted. (Motion seconded.)

THE PRESIDENT.—I would like to hear some discussion. At the meeting of the State Chairmen the other night there was a great deal of difference of opinion; in fact, the preponderance of opinion was that it would be a good thing to let things go as they are.

DR. CRAWFORD BOST, San Francisco.—It appeared to many of the State Chairmen the other night that perhaps this was a hasty movement. There is a movement westward and it seems we should give consideration to geographic lines. In addition to the slide, we should see a relief map of the country. Let us make more chairmen, if you want equal representation.

THE PRESIDENT.—I would like to correct what Dr. Bost said. This is not the recommendation of the Executive Board, it is the recommendation of a special committee which was appointed to make the study. We have not polled the Board but I know there is a great division of sentiment.

THE SECRETARY.—There is no greater increase in the Academy of Pediatrics in California than there is in New York. There are not as many members in the western group as there are in New York, and as yet we have not heard anything from them.

DR. PARK WHITE, St. Louis, Mo.—As the one State Chairman who voted in favor of this proposition, I should like to say something. If we can do anything to abolish sectionalism in the Academy, we ought to do so. I am in favor of the proposition.

THE SECRETARY.—I do not want anyone to get the impression that I am sold on this proposition. It would be simpler for me as secretary of the Society to get along as we have gone on for many years, but in fairness to the membership they should have an opportunity to give an answer.

DR. WHITE.—We have enough members present today to avoid the need for circularization. I move for a vote.

DR. M. K. WYLDER, Albuquerque, N. M.—There is a big shift in population all over the country. We, in Region IV, have lived there for so long that we like each other and we do not want our old lines broken up. I believe that right now is not the time to undertake this thing. I would like to move that the thing be laid on the table until next year. (Motion seconded.)

(The vote on the motion to table was taken and the motion was lost.)

THE PRESIDENT.—Are you ready to vote on the original question, to adopt the report of the Committee? All in favor of the proposed motion please rise. (The vote was 110 in favor, 98 against.)

I think under any system of redistricting the Academy will live. This makes necessary a meeting of the Executive Board this afternoon to set up the new order.

We will ask for a report from the Editorial Board of the JOURNAL.

DR. BORDEN VEEDER.—Some sixteen years ago when the Academy was organized, one of the things that it needed was an official organ. A Committeee was organized to see if such a journal could be found. An arrangement finally was made with The C. V. Mosby Company, whereby the Company would undertake the publication of the JOURNAL OF PEDIATRICS, standing all of the losses and receiving any profits. The Academy was to have full charge of the editorial direction of the JOURNAL. None of us had an idea that the JOURNAL would some day become a profitable venture. For a few years, The C. V. Mosby Company lost financially, but in recent years it is obvious that the Company has made a profit. The title of ownership has been always with the Company.

A year ago, a discussion came up in the Editorial Board as to whether or not some financial return from the JOURNAL should go to the Academy. The matter was discussed with The C. V. Mosby Company, and a special committee was appointed to go into the question of ownership of our own journal. The C. V. Mosby Company has made a proposition which would give to the Academy a certain amount of money each year, depending upon the number of advertising pages carried in the JOURNAL. The Company would still own the JOURNAL. The Editorial Board came to the conclusion after long and detailed study and much thought, that the time has come when the Academy should own its own journal. There are two or three methods by which the Academy can own its own journal. One is that it can go into the publishing business, which by all odds is most profitable. Some journals, like the *Annals of Internal Medicine* are owned and operated by their sponsoring societies. Other societies own their own journals but do not look after the business arrangements and arrange with a publisher to conduct the business of the journal on a certain percentage basis or on a certain fee system, while the journal remains the property of the organization. For certain technical reasons the Committee came to the conclusion that it was not practical at the present time for the Academy to undertake the management of the journal through its own office. Two firms were contacted by the Committee and terms were outlined by these firms. Finally the Edi-

torial Board came to the conclusion that it was advisable to accept the plan outlined by Charles C. Thomas, Publisher, of Springfield, Ill., and consequently made certain recommendations, which you will find on page 8 of the Report of the Executive Board, to the Board at its meeting.

There are certain things that must be made clear. Our subscriptions to The C. V. Mosby Company for the Academy as a group runs from July 1 to July 1. Consequently, on the first of July under this plan we terminate our contract or agreement with The C. V. Mosby Company and the JOURNAL OF PEDIATRICS will no longer be the official journal of the American Academy of Pediatrics. It will not be possible to start the new journal before January, 1948, so there will be a lapse of six months without a journal as the official organ of the Academy.

We look on this new journal as an investment for the Academy. There is every reason to believe that in future years the Academy will receive a substantial return on its investment. This will not be true at the start. The Academy is responsible for any loss that may occur as well as being entitled to any profit that may be made. It is necessary for the first year or two, maybe longer, maybe less, to increase the subscription rate for members of the Academy to $10.00 a year. This is due very largely to the increase in costs in printing in the last year. The cost of printing and paper alone has gone up 20 to 25 per cent. We have recommended that a subscription rate be placed on the new journal at the rate of $10.00 per member. This year it will be only five dollars because the journal will not start until the first of January. Should there be a profit from the journal in future years, that profit will first be used to reduce the subscription rate to members of the Academy.

After thoroughly going over the matter, this was the recommendation of the Editorial Board to the Executive Board, and the Executive Board agreed to these recommendations. The present Board of the JOURNAL OF PEDIATRICS appointed by the Executive Board of the Academy resigned as of July 1, when the JOURNAL OF PEDIATRICS will no longer be the official journal of the Academy. This same Editorial Board was requested by the Executive Board to undertake the development of the new journal.

THE PRESIDENT.—We have been asked by the officers of the International Congress that time be given for a report. Dr. Helmholz will present it.

DR. HELMHOLZ.—I think you will all be interested to know a little more about the International Congress which will be held in New York, July 14-17, 1947. The second International Congress on Pediatrics was held in Stockholm in 1930, the third in London, the fourth at Rome. At the fourth Congress an invitation was extended to hold the next one in America. The invitation was accepted and plans were made to hold it in Boston in 1940. The development of World War II forced cancellation of the plans. In 1938 at the meeting of the Academy held in Del Monte, the Academy voted to assess its membership $10.00. With the onset of World War II, the Executive Board of the Academy voted to return the $10.00 as a credit on yearly dues. After World War II was over, the executive group of the International Congress, depleted by the death of Dr. Blackfan, communicated with a large number of American pediatricians who voted in favor of holding the International Congress in New York, and Dr. L. E. Holt, Jr. was named as Executive Secretary. The difficult question to answer was whether it should be held early or later. Against holding the Congress at an early date was the political restrictions of travel and the financial difficulties, the hopelessness of the financial basis in Europe and the inability of the Europeans to take part in the program. In order that we might have some idea of how the people in Europe felt about it, we wrote to forty European pediatricians and with one or two exceptions they were all in favor of holding the Congress at a very early date. We were interested in knowing other opinions that led us to contact Dr. Alan Gregg of the Rockefeller Institute who had just returned from a trip to Europe and Asia. In talking with him he was very decided that the Congress be held immediately. The fact that the Rockefeller Foundation is making a substantial donation to bring the men over showed that Dr. Alan Gregg was willing to back up his opinion.

He felt that the medical schools in Europe had from three to five times as many students registered as ever before, and only if the pediatricians came over this year would it be possible for them to get away from their work. He also felt that we could give these pediatricians an opportunity to see the development of pediatrics in recent years in this country.

The question of the contribution that the Europeans might make was also discussed. A great deal of work has gone on in England, Switzerland, and Sweden. Experimentally, a great deal of work has been going on in the occupied countries, which started in the Underground and has spread into many places. Dr. Gorter was able to continue his work in Holland in spite of the fact that he was confined to a wheel chair. It seemed to us, in view of the work that was going on, that we could get up an excellent program and that we should hold the Congress. We had decided on September, 1947. We were already going ahead to hold it then when we got information from the hotels in New York that the United Nations were requesting 5,000 extra rooms for September, 1947, so that we could not hold the Congress at this time. So it was decided to hold it in New York in July. While not ideal, that was the time we could be assigned sufficient rooms to take care of the Congress.

From the program that Dr. McIntosh has worked out I feel sure that we will have a very interesting meeting that will be participated in by pediatricians of all the various countries. The American contribution to the program will be largely in the scientific exhibits. Dr. Mitchell of Memphis and Dr. Schwentker of Baltimore, cochairmen of the exhibit committee, have prepared a complete survey of the progress made in the last ten years in American medicine. We expect to have about 175 exhibits, all carefully catalogued so as to make them available in the foreign language. They are trying to have tours for the visitors to the seacoast and as far west as Chicago and St. Louis. We feel we will be able to give these visitors an excellent view of American pediatrics.

The American Pediatric Society, the Section on Pediatrics of the American Medical Association, and the Society for Pediatric Research have all made contributions to the financial support of the Congress, according to their resolutions. I think at this time the Academy should determine what it will do with regard to the Congress.

THE PRESIDENT.—Since they are associated to some extent, I will ask for a report on the proposed meeting of Region V for delegates from Central and South America, to be held in Washington just prior to the International Congress. Dr. Grulee, will you tell us something about it?

THE SECRETARY.—We will hold the Pan-American Congress in Washington July 9-12, ending on Saturday, the 12th, at the Mayflower Hotel. We are now writing to the men in Latin America of this meeting. I have a list of some 4,500. We have to reach all we can. We do not expect more than 250 to 300 to attend. We are planning some entertainment for them. We will not attempt to have and scientific exhibits. Dr. Hurtado has prepared a program which will be purely and simply a Latin American, United States, and Canadian program. There will, of course, be nothing from Europe. The cost of that meeting will approach $10,000.00. It has not been entirely covered yet. We have hopes.

DR. STRINGFIELD.—In October of last year I had a meeting of our state chairmen in Washington, at which time we discussed the Fifth International Clinical Congress. At that time it was the unanimous opinion of the State Chairmen that the holding of an International Congress at this time was premature. They were also of the unanimous opinion that if and when an International Congress was held, the pediatricians of this country should get behind it to the best of their ability and that we should assess each member $10.00 in order to assist in financing this venture. Therefore, Mr. President, I would like to move that the pediatricians of this country make every effort possible to assist in making the Fifth International Congress a success, and that the members of the Academy assess themselves $10.00 to help defray the expenses associated with this undertaking. (Motion seconded and carried.)

THE PRESIDENT.—There are several resolutions which have been presented. I will ask the Secretary to read them.

THE SECRETARY.—The first is presented by the State Chairmen:

"*Resolved,* that the State Chairmen of the Academy of Pediatrics recommend that the attention of the appropriate officials be called to the necessity of raising the salaries of Public Health personnel at local, state, and federal levels in order to obtain qualified physicians for these positions."

I move its adoption. (Motion seconded and carried.)

The second resolution reads as follows:

"Your Committee on Mother's Milk Bureaus requests the Academy at this meeting to give its official endorsement and support to a national movement to encourage breast feeding of infants."

JULIUS H. HESS, Chairman
CARL H. LAWS
MINER C. HILL
CLEMENT A. SMITH
WILLIAM J. ORR

I move its adoption. (Motion seconded and carried.)

The following resolutions relate to this meeting in Pittsburgh.

"*Be it resolved,* that the American Academy of Pediatrics express its sincere appreciation to the local members in the Pittsburgh area and to Drs. W. W. Briant, Jr., E. R. McCluskey, and H. T. Price for the splendid cooperation in the planning and conduct of the annual meeting held at the Hotel William Penn Feb. 24 to 27, 1947."

I have never received such cooperation as I received in Pittsburgh. I move its adoption. (Motion seconded and carried unanimously by a rising vote.)

"*Be it resolved,* that the American Academy of Pediatrics express its sincere appreciation of the superior manner in which the Pittsburgh Convention Bureau handled the hotel registrations for the annual meeting of the Academy held Feb. 24 to 27, 1947."

I move its adoption. (Motion seconded and carried unanimously.)

"*Be it resolved,* that the American Academy of Pediatrics express its sincere appreciation to the management of the Hotel William Penn for the splendid cooperation of all the Hotel Executives, as well as the employees, and especially to Mr. William F. Kirk, Sales Manager, Mr. J. D. Stroup, Assistant Sales Manager, and Mr. Louis Berti, during the preparation for and the period of the annual meeting of the Academy held Feb. 24 to 27, 1947."

I want to say my experience with these gentlemen has been entirely satisfactory. I move the adoption of the resolution. (Motion seconded and carried unanimously.)

"*Be it resolved,* that the American Academy of Pediatrics sincerely appreciates the courtesy of the Libby, McNeill and Libby Company, The Mennen Company, Mead Johnson and Company, H. J. Heinz Company, the Joseph Horne Company, and the University of Pittsburgh for providing the special events for members and their wives attending this meeting."

I move its adoption. (Motion seconded and carried unanimously by a rising vote.)

THE SECRETARY.—The following is the report of the Nominating Committee:

Report of the Nominating Committee

Recommendations.—

For Vice-President (President-elect):
John A. Toomey, Cleveland, Ohio

If the redistricting is *not* passed by the members:
For Chairman of Region IV:
Vernon W. Spickard, Seattle, Washington

If the redistricting *is* passed by the members:
For District I, Oliver L. Stringfield, Stamford, Conn. (1 year).
For District II, Paul W. Beaven, Rochester, N. Y. (2 years).
For District III, Philip S. Barba, Philadelphia, Pa. (3 years).

For District IV, Warren W. Qillian, Miami (Coral Gables), Fla. (1 year).
For District V, James W. Bruce, Louisville, Ky. (2 years).
For District VI, George F. Munns, Winnetka, Ill. (3 years).
For District VII, Thomas J. McElhenney, Austin, Tex. (1 year).
For District VIII, Vernon W. Spickard, Seattle, Wash. (2 years).
For District IX, The representative will be determined by a vote of the Latin-American members at the meeting of the Pan-American Congress in Washington, July 10 to 13, 1947 (3 years).

Respectfully submitted,
EDWARD B. SHAW, Chairman
PRESTON A. MCLENDON
HOWARD J. MORRISON
WYMAN C. C. COLE

THE PRESIDENT.—You have heard the report; are there any further nominations? (No nominations were made.) If not, I should like a motion to accept the Committee's report.

DR. VEEDER.—I so move, that the report be accepted and that the Secretary be instructed to cast the affirmative ballot for those who have been proposed by the Nominating Committee. (Motion seconded and carried unanimously.)

The ballot was cast and the President declared the nominees elected.

THE PRESIDENT.—It now becomes my pleasure to install the President for the coming year, Dr. Lee Forrest Hill of Des Moines. I will ask Drs. Love and Henske to escort Dr. Hill to the platform to receive the gavel.

DR. HILL—I cannot begin to tell you how much I appreciate the honor conferred upon me by making me your President. The individual who would not be flattered by that would have something wrong with him. I am not unaware of the problems that confront the Academy in the years ahead. It is a healthy sign when we have problems. That is what I am interested in. I want to assure you on the part of the Executive Committee and myself that we will settle the problems of the Academy and keep it going the best we can.

I think we should give a standing vote of appreciation to our past President, Dr. Jay I. Durand.

There being no further business, on motion duly made and seconded, the meeting adjourned *sine die*, at 4:30 P.M.

The Academy Study of Child Health Services

REPORT OF THE COMMITTEE ON THE STUDY OF CHILD HEALTH SERVICES

The Academy Study is now in full flight in its two-phased quest for factual information on all aspects of health services in every state and pediatric education in every medical school and teaching hospital throughout this country. It has passed from its embryonic stage: the red hot baby has passed through a phenomenal period of growth and development, reaching in stature and efficiency almost that of our able Director, Dr. John Hubbard.

The present stage of the Study of Child Health Services is a critical one. It requires the continued, able, and enthusiastic support of every member of the Academy and each State Chairman. Now is the most important and difficult part of the race. Endurance and fitness will be determining factors. Dr. Hubbard and his central executive staff will stand ready to coach you as you reach first base and bring every possible support to enable you to reach home plate. Many of you have put exhausting work into this Academy project. It is not surprising that some of you have grown weary in its accomplishment. But unless you continue your efforts during this last critical phase, the game will not be won.

You will be interested to know that the Study has been organized in all states but one and we expect this one state to follow soon. About a dozen states have completed the collection of information and have sent the questionnaire schedules to the Central Office for statistical analysis. There are many other states that are nearing completion of the Study. It is anticipated that by the beginning of summer the desired information will have been obtained from all states. Indeed, it is essential that the collection of information be completed by July 1, in order that the data may be tabulated and reported by the end of this year or early in 1948, which is the Academy's goal.

During the past year it has become evident to your Committee and its Executive Staff that in addition to an over-all national report, which is what was originally intended, material should be returned to State Chairmen and their Advisory Committees in order to serve as a basis for recommendations and plans to be formulated at the state and local level. With an appreciation of the importance of state reports, a great deal of time and effort has been put into a preliminary draft of the Study in North Carolina, our Pilot State. This preliminary draft has been prepared for a twofold purpose: so that State Chairmen may have a preview of the information which will be available for all states, and so that the committee appointed by the North Carolina Pediatric Society to draw up a final report may select from the formidable array of tabulated material, those items which appear important for local planning.

Most State Chairmen will be familiar with the table forms which are included in this draft, since the tables constitute a revision of the table forms which were discussed in detail last fall at the regional meetings held in Chicago, San Francisco, and Washington. The data for North Carolina have now been entered in these tables. In the final North Carolina report certain of the tables will be omitted entirely; certain others will be transferred from the appendix to the text to permit easier reference to them. In this draft, all the basic tables have been put together in the appendix, in order that State Chairmen may see the amount and type of data which will be tabulated for each state and from which each chairman may select those facts that, for his particular state, seem sufficiently important to include in his published report.

The Executive Staff has not been concerned with recommendations arising from the facts which the Study has revealed in North Carolina. This is a responsibility which belongs to the duly appointed Committee, which, we hope, will reduce the overwhelming mass of factual data to more appropriate dimensions, as well as prepare the recommendations to serve as a basis for a continuing program.

The preparation of this preliminary draft of the North Carolina report is no small accomplishment and emphasizes the effective working relationship which has been established during the course of this Study between the Academy of Pediatrics, the Children's Bureau and the U. S. Public Health Service. This may be said to represent one of the first fruits of the Study, which, in the long run, may well prove to be one of its most significant features, for we have set the stage upon which similar cooperation may continue in implementing the results of this fact-finding study.

The analysis of the factual data in sufficient detail to be of use for local planning in North Carolina and in all other states has greatly increased not only the work of the Central Office but also the cost of the Study. A year ago there was about $10,000 in the kitty for the conduct of the Study. That was all, except hope. Now, by virtue of the generous support of many of the Academy's loyal friends, the expenses of the Study have been met to the tune of somewhat over $1,000,000. I wish to take this opportunity to express the gratitude not only of your Committee but the Academy as a whole to those who have helped us so generously.

We have received a grant of $116,000 from the National Foundation for Infantile Paralysis. The National Institute of Health has given us $128,550.00, with the promise of more to come for the statistical analysis. We have received a grant from the Field Foundation of New York, and contributions from the Mead Johnson Company, M. & R. Dietetic Laboratories, The Pet Milk Co., Carnation Company, Lederle Laboratories, The Borden and The Mennen Companies. I wish also to congratulate the State Chairmen for the success with which they have financed their own state programs from public and private sources to a total figure of about $450,000.

In addition to these State studies, which are now nearing completion, the second major phase of the Study has been developed during the past year. I refer to our evaluation of Pediatric Education in all the seventy medical schools of the country and in the teaching hospitals. Dr. John Mitchell of Philadelphia has been appointed as Director of this branch of the Study and is now touring the country spending two or three days in each medical school. A subcommittee has been appointed to develop this part of the Study. Dr. James Wilson is its chairman. It consists of six additional professors of pediatrics, one from each of different areas of the country, so that each member of the Committee may be responsible for the Study in about ten medical schools in his area.

Your Committee has been greatly concerned about the future of the Study. The question is, what are we going to do with the factual data? Through the wisdom of your Executive Board, a follow-up Committee of Nine has already been formed. After our final report is made, this new Committee will make recommendation on a national level—further cooperative efforts with national groups and act as advisers on the state level. The function of the Committee cannot be entirely envisaged, but it is fair to say that the improvement of child health in this country may rest in its hands. The members of this Committee are Dr. James Wilson, Chairman, Drs. Powers, London, Poncher, Kennedy, Sisson, Thelander, Wheatley, and Webb. This Committee has already met, and it is reasonable to express the hope that the Director of the first Committee will continue in the activities of the Academy through this new group.

Respectfully submitted,
WARREN R. SISSON, Chairman.

The Social Aspects of Medicine

The article on the Health Insurance Plan of Greater New York by Dr. Ann Kent and Dr. Dean A. Clark, the Director, was specially prepared for this column. As will become immediately apparent to the reader, the Plan possesses noteworthy features: First, it brings to the subscribers the finest kind of comprehensive medical care, including preventive care. Most of the medical plans in operation in this country furnish only general practitioner care. Second, the Plan furnishes good compensation to the physicians working under it; for example, it allows for $10,000 salaries to its full-time physicians. The Plan embodies, therefore, two principles which must be at the basis of any sound medical care plan, namely, the supply of all the advantages of preventive medical care and specialist service to its clientele and adequate financial compensation coupled with security to its physicians. I might point out additionally that it possesses the great merit of retaining the general practitioner in the hub position of family doctor.

The Plan has, of course, a great deficiency, in that it does not include the lowest income groups, who still remain without the pale; indeed, it suffers greatly from its sharp limitation to certain industrial groups within the $5,000 income level. How can such kind of comprehensive medical care be extended so that it will include all who need it? That is the great question. Senator Taft is quoted in Medical Economics as saying: "Moreover, the man who is helped by the State must not be quite so well off as the man who earns his own living and stands on his own feet." (Medical Economics, vol. 24, p. 81, 1946.) I hope that this reactionary, undemocratic point of view is as repugnant to the readers of the column as to me. In the first place, the best and most comprehensive medical care is more required at the lowest economic levels than at any others. If the lowest income groups could have the very best medical care, some of them would be lifted out of the indigent category, for in many instances they are indigent because of relievable circumstances, chief among which is poor health. Further, the down-and-out groups furnish the fertile soil for communism and the way to erradicate communism is to remove the conditions which breed it. In the second place, the term "medically indigent" is a relative one denoting merely a fractional relationship between the degree and duration of illness in the numerator and ability to pay in the denominator. Most of us would become medically indigent if there were in our families illnesses of sufficient magnitude and duration. Even in a doctor's family the bills for hospital and nursing care can be disabling. If Senator Taft was correctly quoted, his remark implies that the man who must be helped by the State suffers from inferior character. His remark is reminiscent of the refrain:

> "Rattle his bones over the stones
> He's only a pauper whom nobody owns."

In the last verse of "The Pauper's Last Ride," the refrain changed to: "He is a pauper whom only God owns."

Before concluding, I might point out another great deficiency in the H.I. Plan, namely, that the required hospital insurance covers only catastrophic illness. The Plan, therefore, does not relieve the subscribers from the very worst illness situations which can occur, i.e., even under the Plan a subscriber may become "medically indigent."

In summary, the criticisms of the Plan can all be reduced to the single criticism of limitation of scope, not incorrectness in design. Perhaps its success will make its enlargement and extension a natural evolution.

E. A. P.

MATERNAL AND CHILD HEALTH BENEFITS UNDER THE HEALTH INSURANCE PLAN OF GREATER NEW YORK

ANN KENT, M.D., M.P.H.,* AND DEAN A. CLARK, M.D.†
NEW YORK, N. Y.

Within the past five or six decades there has been a tremendous widening of the field of medical knowledge. Complete medical care can no longer be given by any one physician. A general physician today must work with one or more of the increasing number of specialists in order to provide his patients with care which meets the highest modern standards. The cost and complexity of this kind of care have led to the development of group practice by physicians. This system of practice calls for the close professional cooperation of general physicians and specialists sharing equipment and personnel. Group practice first grew out of the association of doctors in charity clinics and teaching hospitals. Many well-known groups are now in operation, not primarily associated with hospitals, such as groups in private practice, or associated with consumer cooperatives or with industrial concerns. There are many different ways of financing group practice, as, for instance, by endowments and gifts, public funds, subsidies from government or industry, and finally by fee for service or by a plan of periodic prepayments to the group which undertakes to give care.

The Health Insurance Plan of Greater New York combines the private practice of group medicine with a system of financing by means of periodic prepayments by subscribers to the Plan. The HIP is incorporated as a nonprofit membership corporation; it is a voluntary undertaking. Eligibility for enrollment is limited to persons whose income is $5,000 or less. Enrollment is restricted to employed groups of twenty-five or more, and each employed group must constitute 75 per cent or more of an employment unit: a whole firm or some department or subdivision thereof. The subscriber's spouse and unmarried children under 18 years of age are also eligible for benefits. There are three classes of premium: 56 cents per week for an employee without dependents, $1.12 per week for an employee with one dependent and $1.68 per week for an employee with two or more dependents. In each case, the employer is expected to pay at least half of the premium. Every subscriber to HIP is required also to belong to a prepayed hospitalization plan.

The benefits to which an HIP subscriber is entitled include complete medical, surgical, and obstetrical care in the home, office, or group center and in the hospital; laboratory and x-ray procedures; physiotherapy and radiotherapy; visiting nurse service in the home and ambulance service from home to hospital. Insured persons are also entitled to preventive measures such as health education, periodic health examinations and immunizations. Benefits not included are cosmetic surgery, treatment for acute alcoholism and drug addiction, and care for tuberculosis, psychiatric illness and other chronic illnesses which require treatment in institutions other than hospitals for general care. Drugs, appliances, and eye glasses are not supplied. Dental care is not included at the present, but it is hoped that this service may be started for children of subscribers before long.

The medical service is provided by physicians who have organized themselves into groups which have met the medical standards drawn up by the HIP Medical Control Board. Any physician licensed in New York State is eligible to participate in the HIP program, provided that he meets the minimum medical standard and becomes affiliated with a medical group. He is not required to give up his private practice. The standards for individual physicians vary according to whether the man wishes to be a general practitioner or a specialist in his group. The group as a whole must be large enough eventually to provide medical care for a minimum of 10,000 people, allowing for a maximum ratio of one full-time

*Supervising Physician, Secondary School Health Services, New York City Health Department.
†Medical Director, Health Insurance Plan of Greater New York.

physician or the equivalent in part-time service for each 800 insured persons. In each group twelve basic specialties must be covered and in addition the group must include five to six general practitioners. The basic specialties are: internal medicine, general surgery, obstetrics and gynecology, pediatrics, otolaryngology, ophthalmology, urology, orthopedics, dermatology, neuropsychiatry, radiology, and pathology.

The individual physicians and the group as a whole are passed upon by the Medical Control Board of the HIP. This Board is made up of physicians appointed by the Board of Directors of HIP and its function is to promulgate and maintain high professional standards in the medical groups. It includes representatives of the five county medical societies of New York City and the New York Academy of Medicine. Before a group is ready to give service it must provide either a medical center to house all or part of its doctors or an administrative headquarters where the business of the group can be transacted, while the individual physicians provide service in their own offices. The contract which the group signs with the HIP contains a clause, however, in which the group undertakes to provide a medical center as soon as it becomes possible to do so. In return for providing the medical service outlined in the foregoing paragraphs, the group receives from HIP $19.20 per insured individual per year. This allows for an average net income of about $10,000 for each full-time physician of the group. The HIP pays the capitation to the group as a whole and does not undertake to regulate its distribution among individual members. The income of the group physicians are therefore subject to the groups internal arrangements and may depend upon age, experience, type of practice, amount of time devoted to the group, and other factors.

Subscribers to the HIP have a free choice of which group to join. Prospective enrollees are given booklets in which the names and addresses of the members of the various medical groups are listed. Subscribers are asked to choose from among those groups which have agreed to serve the area in which the subscriber's residence is located. There are now twenty-two medical groups, including some 700 physicians, providing service to the initial HIP subscribers and dependents. In order to assure continuity of service, once a subscriber has chosen a group from which he wishes to obtain service, he is asked to select as his family physician one of the general physicians of the group. This general physician will be the subscriber's family doctor from then on and will call upon the services of the group's specialists and facilities as needed.

The foregoing has been discussion of the HIP in general terms. Specific advantages to maternal and child health should be emphasized. There is no waiting period for coverage for obstetrics, and there is no limit to the duration or type of obstetrical care. Care of the infant is assumed from the time of birth; the first ninety days of life are not excluded as is the case in some other insurance plans. Overloading of physicians is guarded against by limiting the load to a maximum ratio of 800 insured persons per full-time physician or his equivalent in part-time service.

Continuity of medical service is very often lacking when families, particularly in low income groups, attempt to secure medical care without guidance. They frequently shop around from private physician to private physician and from one clinic to another and such preventive medical care as they do receive is practically always given in a free clinic by doctors who have no contact with them when they are ill. This very inefficient type of care is eliminated under the HIP because the family physician will bear the responsibility for the care of the subscriber and his family in sickness and in health.

The family physician is free to make the fullest possible use of his group's specialists without additional charge to his patients. Ready availability of specialists' services is particularly valuable in the field of maternal and child health because of the great frequency with which the need for this kind of consultation arises in general practice. Although, as the HIP groups are now constituted, it may not be possible for the obstetrician, if he is the only one in the group, to give all the prenatal care himself, every group's obstetrician has supervision over and responsibility for all obstetrical services including pre- and postnatal care and is available for the actual delivery. The group's pediatrician is likewise avail-

able for consultation in cases of illness among children of subscribers and, in most of the medical groups all child care will be provided by pediatricians. In any case, it will be the pediatrician's responsibility to see that the physicians of the group give child care according to the best modern standards.

Hospitalization within the limits of the community's resources is assured because each HIP subscriber is required to belong to a hospital plan as a condition of being accepted for HIP medical benefits.

The HIP will conduct a health education program among its subscribers emphasizing preventive medical care and other factors in healthy living for everyone at all ages, and the participating physicians are urged to make provisions for such care in arranging the work of the groups.

It should also be noted that the Plan is not limited to indigents alone. By setting the top income eligible for enrollment at $5,000, families are included who otherwise probably receive very mediocre medical care; they cannot afford to buy the best available and they will not accept the often excellent care given in free clinics. On the other hand, the rather high premiums required to finance the HIP do not become a deterrent to potential subscribers in the lower income brackets because of the fact that in each case the subscriber's employer shares at least half of the cost. This sum, as previously stated, does not increase beyond the amount required to insure an employee and two dependents, regardless of the actual size of the subscriber's family. There is very great interest in this policy of sharing the cost because most employers have come to realize the long-range wisdom of aiding their employees to secure good health service, because they feel that employees are more loyal and efficient when they are in good health themselves, free from concern over family medical cost, and have a feeling of security regarding health problems in general.

In conclusion, the comprehensive program of the HIP offers great advantages, both in preventive medicine and in therapy, to maternal and child health. The experience that will accumulate when the program is operating on a large scale will be of great value in defining more clearly the health needs of mothers and children and in demonstrating practicable methods of meeting these needs.

Communication

Dear Dr. Veeder:

The newly appointed Committee on Hospitals and Dispensaries of the American Academy of Pediatrics has been asked to study construction standards for Nursery Departments, Pediatric, and Contagious Disease units, as set forth in the Hospital Survey and Construction Act (Public Law 725—Seventy-ninth Congress).

To assist the Committee in formulating recommendations to the proper authorities for additions or changes, it seemed appropriate to publish these standards and to request suggestions and criticisms from members of the Academy, pediatricians, and general practitioners interested in developing plans, under the provisions of the Act, for hospital construction in their local communities. It is to be emphasized that these standards are minimum requirements for construction and equipment as required by the Federal Hospital Council and are in no way concerned with regulations for operation or management of pediatric units.

The following standards for Pediatric and Contagious Disease units are copied from Title 42—Public Health, Chapter 1—a reprint from the Federal Register, Division of Hospital Facilities:

Nursery Department

Full-term nursery:

Area required: Not less than 24 square feet per bassinet, 30 square feet recommended.

Number of bassinets: No more than 12 bassinets in each full-term nursery, 8 recommended.

Examination and workroom: One examination and workroom between each two full-term nurseries.

Premature nursery (to be provided where four or more premature bassinets will be required):

Area required: 40 square feet per bassinet.

Number of bassinets: Not more than six in each premature nursery.

Each premature nursery to have own work areas.

Suspect nursery:

Area required: 40 square feet per bassinet.

Number of bassinets: Approximately 20 per cent of full-term bassinets. Not more than 3 bassinets in each suspect nursery.

Workroom: One workroom for each two suspect nurseries.

Formula room: Location in nursery area or near kitchen optional.

Contagious Disease Nursing Unit

Patient rooms:

A maximum of two beds in each room separated by a glazed partition.

Patient rooms shall have a view window from corridor.

Each patient room shall have a separate toilet and lavatory in the room.

Each nursing unit shall contain:

Nurses' station

Utility room

Nurses' workroom

Treatment room

Scrub sinks strategically located in the corridor.

Kitchen with separated dishwashing room adjacent

Doctors' locker and gown room
Nurses' locker and gown room
Janitors' closet
Storage closet
Stretcher alcove.

Pediatric Nursing Unit

General:

Each bed in a multibedroom shall be in a clear glazed cubicle.
Each room shall have a lavatory.
Patients' rooms wherever possible should have clear glazing between them and in the corridor partitions.

Minimum area:

80 square feet per bed in two-bed rooms and over.
100 square feet in single rooms.
40 square feet per bassinet in nurseries.

Each nursing unit shall contain:

Nursery
Isolation suite
Treatment room
Nurses' station with adjoining toilet
Utility room
Floor pantry
Play room or solarium
Bath and toilet room: with raised, free-standing tub and 50 per cent children's fixtures
Bedpan facilities
Wheelchair and stretcher alcove
Janitors' closet
Storage closet.

It is requested that suggestions for additions and changes, or criticisms of the above standards be forwarded to Dr. John McK. Mitchell, Chairman of the Committee on Hospitals and Dispensaries, Cushman Road and Lancaster Avenue, Rosemont, Pa.

(Signed) Montgomery Blair, Jr., M.D.
for the Committee on Hospitals and Dispensaries.

Academy News and Notes

The following members have been released from military service:

Edward D. Anderson, Minneapolis, Minn. *(Navy)*
Donn James Barber, Greeley, Colo. *(Army)*
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Erratum

In the article by Karp and Teuscher entitled "General Anesthesia in the Difficult Pedodontic Patient" in the March, 1947, issue of the JOURNAL on page 320, the following correction should be made in Table I: for the age group 1 to 2 years under atropine, the dosage should read 0.065 mg.

INDEX TO VOLUME 30

A

Academy news and notes, 110, 221, 369, 482, 639, 760

Acrodynia, infantile, 111 (B. Rev.)

Adamski, Edwin J., Light, J., Hoffman, C., Strickler, C. W., Karelitz, S., Wasserman, L. R., and Moloshok, R. E., 18

Adolescents and children with inactive rheumatic fever, sulfadiazine prophylaxis in, 284

Agerty, Horst A., 82

Agglutinative reaction for hemophilus pertussis following whooping cough and following immunization, 171

Airblock in newborn infant, 260

Allen, John E., and Sontag, L. W., 657

Allergy, evaluation of benadryl, pyribenzamine, and other so-called antihistaminic drugs in treatment of, 583
  treatment of patients with benadryl, 41

American Academy of Pediatrics:
  Proceedings, annual business session, 742
  fifteenth annual meeting, 696
  meetings of executive board, 330, 739
  Round tables, 696, 716

Anderson, Dorothy H., 564

Anemia, fatal sickle cell, in one-month-old infant, case report, 468
  sickle cell, and its differentiation from rheumatic carditis, cardiopathy of, 289

Anesthesia, general, in difficult pedodontic patient, 317

Anomalies, congenital heart, factors in etiology of, 295

Anomaly of double aortic arch, 1, 428

Antonov, A. N. 250

Aortic arch, double, 428
    diagnosis and treatment of tracheal and esophageal obstruction due to congenital vascular ring, 1

Aquado, A., Ballabugia, 111

Athetosis, congenital, A-B blood groups and Rh-Hr blood types in, 64

B

Bakwin, Harry, and Wiener, A. S., 64

Baldwin, Janet S., 67, 284

Barash, Louis, Seligmann, E., and Cohlan, S. Q., 182

Beck, Karl H., Janney, F. R., and Conway, J. P., 459

Benadryl, pyribenzamine, and other so-called antihistaminic drugs, evaluation of, in treatment of allergy, 583
  treatment of allergic patients with, 41

Berg, R. H., 483

Berman, Benjamin, and Talmadge, J., 691

Biggs, Alfred D., and Pontius, G. V., 306

Blair, Montgomery, Jr., 760

Blood groups, A-B and Rh-Hr blood types in congenital athetosis, 64

Boas, Ernst P., 478

Body length and weight, relationship of, of infants at birth to age at which they begin to walk alone, 676
  water, estimation of extracellular and total, in newborn human infant with radioactive sodium and deuterium oxide, 413

Bone marrow infusion in childhood, 400
    reaction in tibia following intramedullary administration of fluids, case report, 324
  tumors, 734

Bones, congenital syphilis: effects of penicillin on rate of healing, 547

Book Reviews:
  Acrodinia infantil, 111
  Compleat Pediatrician, 111
  Infant, Social Medicine, 111
  Methods, Clinic and Laboratory, 111
  Muscle testing, 112
  Opera Paediatrica, 111
  Poliomyelitis—Challenge of Polio, 483
  Social Medicine for Infants, 111

Bradley, Charles, 529

Brain, tumors of, in childhood, 726

Braun, K., Roth, I., and Suesskind, S., 177

Brieger, H., and Jones, J. A., 422

Brown, Edward E., and Wasson, V. P., 455

Bucy, Paul C., 726

Budapest, infantile mortality rate in, in year 1945, 244

Burke, Frederic Gerard, and Ross, S., 157

C

Capillary fragility and menses in rheumatic girls, 455
Carditis, rheumatic, cardiography of sickle cell anemia and its differentiation from, 289
Case, Dorothy M., Erganian, J. A., and Forbes, G. B., 129
Celiac syndrome. VI. relationship of celiac disease, starch intolerance, and steatorrhea, 564
Cephalhematoma, meningitis complicating, case report, 327
Cephalin-cholesterol flocculation in premature infants and children receiving immune globulin, 668
Chapple, Charles C., 710
Child and maternal health benefits under health insurance plan of Greater New York, 756
health services, Academy study of, 359
historical background, 637
purposes and publication of state reports, 214
report of committee on study of child health services, 753
review of progress and preview of planning, 475
in Greek life, nurse and, 205
with follicular cyst of ovary, sexual precocity and accelerated growth in, 686
young, and infant, salicylate intoxication in, 129
Childhood, bone marrow infusion in, 400
infectious hepatitis in, 381
pathology of benign and malignant tumors in, 730
rickettsial diseases of, clinical pathologic study of tick typhus, "Rocky Mountain spotted fever," and murine typhus, "endemic typhus," 495
tuberculous dactylitis in, a prognosis, 146
tumors of brain in, 726
Children and adolescents with inactive rheumatic fever, sulfadiazine prophylaxis in, 284
and infants, genitourinary system, conditions in, 603
premature, receiving immune globulin, cephalin-cholesterol flocculation in, 668
radiological aspects of benign and malignant tumors in, 722
born during siege of Leningrad in 1942, 250
early evidence of psychoses in, with special reference to schizophrenia, 529
intracranial tumors in (abstract), 735
Cholesterol-cephalin flocculation in premature infants and children receiving immune globulin, 668
Cincinnati General Hospital, treatment of acute diarrhea in, during years 1944 and 1945, 45
Clark, Dean A., and Kent, A., 756
Clifford, Stewart H., 640, 696
Cohen, Shirley M., Miller, B. W., and Orris, H. W., 327, 468
Cohlan, Sidney Q., Seligmann, E., and Barash, L., 182
Comment:
Academy grows up, 643
fifteenth annual meeting, 484
women and children and war, 370
Communication, 759
Compleat Pediatrician, 111 (B. Rev.)
Conrad, Elizabeth, Webb, B. D., and Dubs, E. J., 76
Conway, James P., Janney, F. R., and Beck, K. H., 459
Correspondence, 227
Cowie, D. B., Vosburgh, G. J., Hellman, L. M., Flexner, L. B., Wilde, W. S., and Proctor, N. K., 413
Crayons, wax, poisoning due to ingestion of, 422
Cummings, G. D., 706
Cyst, follicular, of ovary, sexual precocity and accelerated growth in child with, 686

D

Dacryostenosis, 302
Dactylitis, tuberculous, in childhood: prognosis, 146
Dale, John H., Jr., 722
Dale, Maurice L., 199
Daniels, Lucille, Williams, M., and Worthingham, C., 112
Dargeon, Harold W., 716
Davenport, Harbert, Salmon, G. W., and Forbes, G. B., 260
Davis, William S., Hyman, M. E., and Ruhstaller, F. D., 55
Davison, Wilburt C., 111
Deficits in diarrhea, 488
DeGara, Paul F., and Mayer, S. A., 171
DeSanctis, Adolph G., and Sullivan, A. M., 91
Deuterium oxide and radioactive sodium, estimation of extracellular and total body water in newborn human infant with, 413

Deutsch, Joyce, Horstmann, D. M., and Havens, W. P., Jr., 381
Diarrhea, acute, treatment of, in Cincinnati General Hospital during years 1944 and 1945, 45
deficits in, 488
epidemic, of newborn as hospital problem, 710
from point of view of epidemiologist and bacteriologist, 706
infant from point of view of clinical investigator, 700
Diphtheria and diphtheria carriers, penicillin in treatment of, 18
Dodd, Katharine, 698, 700
—, Weihl, C., and Rapoport, S., 45
Dogramaci, Ihsan, 672
—, and Green, H., 295
Dopkeen, Saul K., Hechter, O., and Yudell, M. H., 645
Dowling, Harry F., Sweet, L. K., and Howell, M. J., 438
Dubs, Elizabeth J., Webb, Bailey D., and Conrad, E., 76
Dunsky, Irvin, and Lawrence, G., 416
Durand, Jay I., 485
Dyer, R. E., 226

E

Ehrlich, John, 541
Emphysema, interstitial, in newborn infant, 260
Empyema, primary staphylococcus pneumonia, with penicillin as aid in treatment of, 55
Encephalitis associated with herpes zoster, case report, 473
Enteritis, salmonella, in infants, streptomycin treatment of, 182
Enterostomy alone, first case of atresia of ileum, cured by, 679
Erganian, Jane A., Forbes, G. B., and Case, D. M., 129
Erratum, 760
Esophageal and tracheal obstruction due to congenital vascular ring, diagnosis and treatment of, 1

F

Faber, Harold K., and Halpern, B. C., 289
Feld, Harold, Gottlieb, C., and Sharlin, H. S., 462
Fifth international congress of pediatrics, 222
Findlay, Charles W., Jr., Sweet, R. H., and Reyersbach, G. C., 1
Flexner, L. B., Wilde, W. S., Proctor, N. K., Cowie, D. B., Vosburgh, G. J., and Hellman, L. M., 413
Fluids, reaction in tibia following intramedullary administration of, case report, 324
Forbes, Gilbert B., Davenport, H., and Salmon, G. W., 260
—, Erganian, J. A., and Case, D. M., 129

G

Gamble, James L., 488
Gangrene, postscarlatinal, with prolonged prothrombin time, 76
Garrot, Lucien, 111
Genitourinary system, conditions in infants and children, 603
Geren, Betty B., Pratt, E. L., and Neuhauser, E. B. D., 388
Gesell, Arnold, 188, 220
Girls with rheumatic fever, capillary fragility and menses in, 455
Glomerulonephritis, acute, 157
Glycosuria, renal, associated with pentosuria, 416
Goldstein, Hyman, 41
Gordon, Susanna, 428
Gottlieb, Charles, Sharlin, H. S., and Feld, H., 462
Green, Hyman, and Dogramaci, I., 295
Growth, accelerated, and sexual precocity in child with follicular cyst of ovary, 686

H

Halpern, Barbara Cutting, and Faber, H. K., 289
Hardy, Janet B., and Hartmann, John R., 146
Hartmann, John R., and Hardy, J. B. 146
Havens, W. Paul, Jr., Horstmann, D. M., and Deutsch, J., 381
Health control, United States Public Health Service, and development of federal participation in, 106
insurance plan of Greater New York, maternal and child health benefits under, 756
Heart anomalies, congenital, factors in etiology of, 295
block, intraventricular in malnutrition and vitamin B deficiency, 177
disease of sickle cell anemia and its differentiation from rheumatic carditis, 289

Hechter, Oscar, Dopkeen, S. K., and Yudell, M. H., 645
Heinild, Svend, Søndergaard T., and Tudvad, F., 400
Hellman, L. M., Flexner, L. B., Wilde, W. S., Proctor, N. K., Cowie, D. B., and Vosburgh, G. J., 413
Hemophilus pertussis following whooping cough and following immunization, agglutinative reaction for, 171
Hendricks, Walter J., and Peters, M., 72
Hepatitis, infectious, in childhood, 381
Herendeen, Ralph E., 734
Herpes zoster, encephalitis associated with, case report, 473
Hill, Allan J., Jr., Platou, R. V., and Kometani, J. T., 547
Histoplasmin-tuberculin skin sensitivity, lung calcifications and, 657
Histoplasmosis in infancy, 123
Historical background of study of child health services, 637
Hoffman, Charles, Strickler, C. W., Adamski, E. J., Light, J., Karelitz, S., Wasserman, L. R., and Moloshok, R. E., 18
Holland (1944-1945), effects of maternal undernutrition upon newborn infant in, 229
Holley, Edward B., 96
Horstmann, Dorothy M., Havens, W. P., Jr., and Deutsch, Joyce, 381
Howell, M. Jane, Sweet, L. K., and Dowling, H. F., 438
Hubbard, John P., 359
Hyaluronidase in hypodermoclysis, clinical use of, 645
Hyman, Mary E., Davis, W. S., and Ruhstaller, F. D., 55
Hypercalcemia and idiopathic hyperplasia of parathyroid glands in infant, 388
Hyperthyroidism, thio-uracil in childhood, 371
Hypodermoclysis, clinical use of hyaluronidase in, 645

I

Iams, Alexander M., and Keith, Haddow M., 123
Ileum, atresia of, first successful case cured by enterostomy alone, 679
Immune globulin, cephalin-cholesterol flocculation in premature infants and children receiving, 668
Immunization, agglutinative reaction for hemophilus pertussis following whooping cough and following, 171
  pertussis, studies on, 29
Infancy, histoplasmosis in, 123
Infant and young child, salicylate intoxication in, 129
  epidemic diarrhea of newborn, as hospital problem, 710
    from point of view of clinical investigator, 700
    from point of view of epidemiologist and bacteriologist, 706
  hypercalcemia and idiopathic hyperplasia of parathyroid glands in, 388
  mortality rate in Budapest in year 1945, 244
  newborn, human, estimation of extracellular and total body water in, with radioactive sodium and deuterium oxide, 413
    in Holland (1944-1945), effects of maternal undernutrition upon, 229
    intestinal obstruction of, 306
    round table discussion on infection, of, 696
  one-month-old, fatal sickle cell anemia in, case report, 468
  premature, weighing 820 grams, report on, 199
  social medicine of, and measures for protection of first year, 111 (B. Rev.)
  syphilis in, 698
Infants and children, genitourinary system, conditions in, 603
    radiological aspects of benign and malignant tumors in, 722
  premature, and children, receiving immune globulin, cephalin-cholesterol flocculation in, 668
  relationship of body weight and body length of, at birth to age at which they begin to walk alone, 676
  streptomycin treatment of salmonella enteritis in, 182
Infection in newborn period (Round table discussion), 696
Insurance plan, health, of Greater New York, maternal and child health benefits under, 756
Intestinal obstruction, of newborn infant, 306

J

Janney, F. R., and Williams, L. P., 371
—, Francis R., Conway, J. P., and Beck, K. H., 459
Jones, J. Albright, and Brieger, H., 422
Judd, James R., 679
Jundell, I., Lichtenstein, A., and Wallgren, A., 111

K

Karelitz, Samuel, Wasserman, L. R., Moloshok, R. E., Strickler, C. W., Adamski, E. J., Light, J., and Hoffman, C., 18

Karp, Mary, and Teuscher, G. W., 317

Keith, Haddow M., and Iams, A. M., 123

Kent, Ann, and Clark, D. A., 756

Kerpel-Fronius, E., 244

Kimmel, George C., 686

Kometani, John T., Hill, A. J., Jr., and Platou, R. V., 547

Kretschmer, Herman L., 603

L

Lawrence, Grace, and Dunsky, I., 416

Leningrad in 1942, children born during siege of, 250

Lichtenstein, A., Jundell, I., and Wallgren, A., 111

Light, Jacob, Hoffman, C., Strickler, C. W., Adamski, E. J., Karelitz, S., Wasserman, L. R., and Moloshok, R. E., 18

Lung calcifications and histoplasmin-tuberculin skin sensitivity, 657

M

Malnutrition and vitamin B deficiency, intraventricular block in, 177

Maternal and child health benefits under health insurance plan of Greater New York, 756

Mayer, Shirley A., and deGara, Paul F., 171

McCormick, George W., 473

Medical care, compulsory prepaid, 478
profession in Sweden, some aspects of, 361

Medicine, social, of infancy and measures for protection of first year, 111, (B. Rev.)

Meeting of executive board of American Academy of Pediatrics, report of, 330

Meningitis complicating cephalhematoma, case report, 327
due to salmonella manhattan, case report, 459

Meningococcemia, acute, 438

Menses and capillary fragility in rheumatic fever girls, 455

Methods, clinic and laboratory, 111 (B. Rev.)

Miller, Bertram W., Cohen, S. M., and Orris, H. W., 327, 468

Miller, M. C., 201

Moloshok, Ralph E., Karelitz, S., Wasserman, L. R., Strickler, C. W., Adamski, E. J., Light, J., and Hoffman, C., 18

Mortality rate, infantile, in Budapest in year 1945, 244

Morvan's syndrome, 96

Mossberger, Joseph I., 113

Muscle, testing of, techniques of manual examination, 111 (B. Rev.)

N

National commission on children and youth at first conference, citizen action for children urged by, 223

Nephrosis, treated with concentrated, low salt, human serum albumin, 91

Neuhauser, Edward B. D., Pratt, E. L., and Geren, B. B., 388

New York, Greater, maternal and child health benefits under health insurance plan of, 756

News and notes, 110, 222, 483
Academy, 110, 221, 369, 482, 639, 760

Norval, Mildred A., 676

Nurse and child in Greek life, 205

Nutrition, under-, maternal, effects of, upon newborn infant in Holland (1944-1945), 229

O

Opera Paediatrica, 111 (B. Rev.)

Orris, Harry W., Cohen, S. M., and Miller, B. W., 327, 468

Oser, Bernard L., and Vollmer, H., 446

Osteoarthropathy, hypertrophic pulmonary, 462

Ovary, follicular cyst of, sexual precocity and accelerated growth in child with, 686

Overall, James C., Peterson, J. C., and Shapiro, J. L., 495

P

Para-aminobenzoic acid, spotted fever treated with, 72

Parathyroid glands in infant, hypercalcemia and idiopathic hyperplasia of, 388

Park, Edwards A., 755

Paterson, Donald, 218

Patient, difficult pedodontic, general anesthesia in, 317

Pease, Marshall C., 639

Pediatrics, developmental, 188
Japanese, experiences with, 82

Penicillin as aid in treatment of primary staphylococcus pneumonia with empyema, 55
effects of, on rate of healing: osseous congenital syphilis, 547
in treatment of diphtheria and diphtheria carriers, 18
Pentosuria, renal glycosuria associated with, 416
Pertussis (*See* whooping cough)
Peters, Michael, and Hendricks, W. J., 72
Peterson, J. Cyril, Overall, J. C., and Shapiro, J. L., 495
Pittaluga, Gustave, 111
Platou, Ralph V., Hill, A. J., Jr., and Kometani, J. T., 547
Pneumonia, primary staphylococcus, with empyema, penicillin as aid in treatment of, 55
rheumatic, 113
Poisoning, due to ingestion of wax crayons, 422
salicylate intoxication in infant and young child, 129
Poliomyelitis: challenge of polio, 483 (B. Rev.)
Pontius, Guy V., and Biggs, A. D., 306
Pratt, Edward L., Geren, B. B., and Neuhauser, E. B. D., 388
Precocity, sexual, and accelerated growth in child with follicular cyst of ovary, 686
Prematurity, report on premature infant weighing 820 grams, 199
Presidential address, 485
Price, Harold W., 302
Prince, George E., 668
Proctor, N. K., Flexner, L. B., Wilde, W. S., Cowie, D. B., Vosburgh, G. J., and Hellman, L. M., 413
Prothrombin time, prolonged, postscarlatinal gangrene with, 76
Psychoses in children, early evidence of, with special reference to schizophrenia, 529
Purpura, congenital thrombocytopenic, 691
Pyribenzamine, benadryl, and other so-called antihistaminic drugs, evaluation of, in treatment of allergy, 583

R

Rapoport, Samuel, Weihl, C., and Dodd, K., 45
Ratner, Bret, 583
Reyersbach, Gertrud C., Sweet, R. H., and Findlay, C. W., Jr., 1
Rheumatic fever, 113
follow-up study on, in subjects previously treated with prophylactic sulfanilamide, 67
girls, capillary fragility and menses in, 455
inactive, sulfadiazine prophylaxis in children and adolescents with, 284
Rickettsial diseases of childhood: clinical pathologic study of tick typhus, "Rocky Mountain spotted fever," and murine typhus, "endemic typhus," 495
Ring, congenital vascular, diagnosis and treatment of tracheal and esophageal obstruction due to, 1
Rocky Mountain spotted fever (*See* typhus, tick)
treated with para-aminobenzoic acid, 72
Rosaria, Sister M., 205
Ross, Sidney, and Burke, F. G., 157
Roth, I., Braun, K., and Suesskind, S., 177
Round table discussions:
infection in newborn period, 696
tumors, benign and malignant, 716
Rowe, Stuart N., 735
Ruhstaller, Frank D., Davis, W. S., and Hyman, M. E., 55

S

Sako, Wallace, 29
Salicylate intoxication in infant and young child, 129
Salmon, George W., Forbes, G. B., and Davenport, H., 260
Salmonella manhattan, meningitis due to, case report, 459
Scarlet fever, gangrene with prolonged prothrombin time, 76
Shizophrenia, early evidence of psychoses in children with special reference to, 529
Seligmann, Erich, Barash, L., and Cohlan, S. Q., 182
Shapiro, John L., Peterson, J. C., and Overall, J. C., 495
Sharlin, Herbert S., Gottlieb, C., and Feld, H., 462
Silverthorne, Nelles, 195
Sisson, Warren R., 754
Skin sensitivity, lung calcifications and histoplasmin-tuberculin, 657
Smith, Clement A., 229

Snedeker, Lendon, 216
Social aspects of medicine, 106, 217, 360, 478, 640, 755
Sodium, radioactive, and deuterium oxide, estimation of extracellular and total body water in newborn human infant with, 413
Søndergaard, Tyge, Heinild, S., and Tudvad, F., 400
Sontag, L. W., and Allen, J. E., 657
Specific gravity, measuring, of small amounts of urine, 672
Starch intolerance, celiac disease and steatorrhea, VI. relationship of: celiac syndrome, 564
State reports, purposes and publication of, academy study of child health services, 214
Steatorrhea, celiac disease, and starch intolerance, VI. relationship of, celiac syndrome, 564
Steiner, Paul E., 730
Streptomycin review, 541
  treatment of salmonella enteritis in infants, 182
Strickler, Cyrus W., Adamski, E. J., Light, J., Hoffman, C., Karelitz, S., Wasserman, L. R., and Moloshok, R. E., 18
Study of child health services, Academy, 102
Suesskind, S., Braun, K., and Roth, I., 177
Sulfadiazine prophylaxis in children and adolescents with inactive rheumatic fever, 284
Sulfanilamide, prophylactic, follow-up study in rheumatic fever subjects previously treated with, 67
Sullivan, Alma M., and DeSanctis, A. G., 91
Sweden, some aspects of medical profession in, 361
Sweet, Lewis K., Dowling, H. F., and Howell, M. J., 438
—, Richard H., Findlay, C. W., Jr., and Reyersbach, G. C., 1
Syphilis in newborn infant, 698
  osseous congenital: effects of penicillin on rate of healing, 547
Syringomyelia, 96

T

Tallerman, Kenneth, 228
Talmadge, Janet, and Berman, B., 691
Tetanus, 195
Teuscher, George W., and Karp, M., 317
Thio-uracil in childhood hyperthyroidism, 371
Tibia, reaction in, following intramedullary administration of fluids, case report, 324
Toxoplasmosis, infantile, 201
Trachea, obstruction of, due to congenital vascular ring, diagnosis and treatment of esophagus and, 1
Tuberculin-histoplasmin skin sensitivity, lung calcification and, 657
Tuberculosis, dactylitis in childhood, 146
Tudvad, Folke, Heinild, S., and Søndergaard, T., 400
Tumors, benign and malignant, in infants and children, radiological aspects of, 722
  pathology of, in childhood, 730
  round table discussion on, 716
  bone, 734
  intracranial, in children (Abst.), 735
  of brain in childhood, 726
Typhus, endemic (*See* typhus, murine)
  murine, "endemic typhus," and tick typhus, "Rocky Mountain spotted fever," clinical pathologic study of, rickettsial diseases of childhood, 495
  tick, "Rocky Mountain spotted fever," and murine typhus, "endemic typhus," clinical pathologic study of, rickettsial diseases of childhood, 495

U

United Stated Public Health Service and development of federal participation in health control, 106
Urine, measuring specific gravity of small amounts of, 672

V

Vascular ring, congenital, diagnosis and treatment of tracheal and esophageal obstruction due to, 1
Veeder, Borden S., 644
Vitamin B deficiency, intraventricular block in malnutrition and, 177
  D, comparative effect of parenteral administration of single massive doses of, in oil-ether vehicle, 446
Vollmer, Hermann, and Oser, B. L., 446
Vosburgh, G. J., Hellman, L. M., Flexner, L. B., Wilde, W. S., Proctor, N. K., and Cowie, D. B., 413

W

Wall, Joseph S., 477
Wallgren, A., Jundell, I., and Lichtenstein, A., 111

Wallgren, Arvid, 361
Walsh, Arthur R., and Zadek, Isadore, 324
War, women and children, 370
Wasserman, L. R., Karelitz, S., Moloshok, R. E., Strickler, C. W., Adamski, E. J., Light, J., and Hoffman, C., 18
Wasson, Valentina P., and Brown, E. E., 455
Webb, Bailey D., Dubs, E. J., and Conrad, E., 76
Weihl, Carl, Rapoport, S., and Dodd, K., 45
Whooping cough, agglutinative reaction for hemophilus pertusses following, and following immunization, 171
immunization, studies of, 29
Wiener, A. S., and Bakwin, Harry, 64
Wilde, W. S., Flexner, L. B., Proctor, N. K., Cowie, D. B., Vosburgh, G. J., and Hellman, L. M., 413
Williams, L. P., and Janney, F. R., 371
Williams, Marian, Daniels, L., and Worthingham, C., 112
Worthingham, Catherine, Daniels, L., and Williams, M., 112

Y

Yudell, Milton H., Hechter, O., and Dopkeen, S. K., 645

Z

Zadek, Isadore, and Walsh, A. R., 324

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INDEX NUMBER

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Table of Contents on 3rd Cover

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. . . when iron and vitamin B complex, in addition to liver, are indicated.

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